CrystEngComm

View Online
Dynamic Article Links

Cite this: DOI: 10.1039/c1ce05155e

www.rsc.org/crystengcomm

PAPER

Crystal structures and chiral recognition of the diastereomeric salts prepared from 2-methoxy-2-(1-naphthyl)propanoic acid†

Akio Ichikawa,*[a] Hiroshi Ono,[b] Takuya Echigo‡[c] and Yuji Mikata[d]

Received 1st February 2011, Accepted 25th March 2011
DOI: 10.1039/c1ce05155e

Published on 21 April 2011 on http://pubs.rsc.org | doi:10.1039/C1CE05155E
Downloaded on 18 May 2011

This paper is the first to report the structures of crystalline diastereomeric salts **8** and **9** prepared from (*R*)-2-methoxy-2-(1-naphthyl)propanoic acid [(*R*)-MαNP acid, (*R*)-**1**] and (*S*)-**1** with (*R*)-1-phenylethylamine [(*R*)-PEA, (*R*)-**7**], respectively. These crystal structures helped elucidate a novel chiral recognition mechanism characteristic of MαNP salts. The less-soluble diastereomeric salt **8** prepared from (*R*)-**1** and (*R*)-**7** formed an ammonium–carboxylate ion pair by means of a methoxy-assisted salt bridge and an aromatic CH···π interaction. The more-soluble diastereomeric salt **9** prepared from (*S*)-**1** and (*R*)-**7** formed an ion pair by a methoxy-assisted salt bridge in which the 1-naphthyl and phenyl groups did not overlap. Instead, salt **9** formed a close ion pair by means of a salt bridge, a CH···O hydrogen bond, and a π···π interaction. These crystal structures suggest that the molecular length from the MαNP plane containing the carboxy and methoxy groups is critical to the crystallisation of diastereomeric salts. The crystal packing in both salts was investigated with regard to the weak interactions (*i.e.*, salt bridges, NH···O and CH···O hydrogen bonds, and aromatic CH···π, CH···π, and π···π interactions). Finally, diastereomeric amides **11** and **12** were prepared from (*S*)-2-methoxy-2-(2-naphthyl)propanoic acid [(*S*)-MβNP acid, (*S*)-**2**] and (*R*)-**2** with (*S*)-1-(1-naphthyl)ethylamine [(*S*)-**10**]. The solution-phase structures of the MβNP amides, and their separation, was investigated by NMR spectroscopy and high-performance liquid chromatography (HPLC). The less-stereochemically demanding and longer 2-naphthyl group made the MβNP amide more flexible and less polar than the MαNP amide. Acid **2** was more efficient than acid **1** in separating amides **11** and **12**.

Introduction

2-Aryl-2-methoxypropanoic acids [*e.g.*, MαNP acid, **1**; MβNP acid, **2**; and 2-methoxy-2-(9-phenanthryl)propanoic acid, M9PP acid, **3**] are powerful chiral resolving agents whose diastereomeric esters can be used to rapidly resolve biofunctional molecules and to elucidate stereochemistry by ^{1}H NMR anisotropy (Fig. 1).[1–4] For these purposes, acid **1** was superior to Mosher's 3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (MTPA, **4**),[5] while the analytical properties of acid **3** were slightly superior to those of **1**.[6] Prior to these studies, Riguera *et al.*[7] and Kusumi *et al.*[8] independently developed the important chiral resolving agent 2-methoxy-2-(2-naphthyl)acetic acid (2NMA, **5**).

Recently, the high crystallinity of 2-aryl-2-methoxypropanoic acids **1–3** and their derivatives was demonstrated.[1,3,9–11] These properties make acids **1–3** useful as stereochemical internal standards for X-ray crystallography, which is considered the most reliable method for elucidating stereochemistry.[1] A herringbone motif[12,13] was observed in both crystalline (*S*)-**3** and a diastereomeric amide derived from (*R*)-**1** and (*S*)-**10**.[11] This motif suggests that aromatic CH···π interactions played an important role in the crystallisation. In addition, the molecular lengths of the acid and alcohol moieties from the MαNP plane were critical in the crystallisation of both the diastereomeric MαNP esters[10] and the MαNP amide.[11]

Fig. 2 shows the conformations of 2-aryl-2-methoxypropanoic acid and its derivatives as elucidated by X-ray crystallography and NMR spectroscopy. In crystalline (*S*)-**3**, the hydroxy and carbonyl groups were *syn*, as were the carbonyl and methoxy groups. The aromatic hydrogen atom at the 10-position and the methyl group were also *syn*.[11] The carboxy groups of (*S*)-**3**

[a]*Division of Insect Sciences, National Institute of Agrobiological Sciences, 1-2 Owashi, Tsukuba, Ibaraki, 305-8634, Japan. E-mail: ichikawa@affrc.go.jp*
[b]*Analytical Science Division, National Food Research Institute, 2-1-12 Kannondai, Tsukuba, Ibaraki, 305-8642, Japan*
[c]*Post-harvest Science and Technology Division, Japan International Research Center for Agricultural Sciences, 1-1 Owashi, Tsukuba, Ibaraki, 305-8686, Japan*
[d]*KYOUSEI Science Center for Life and Nature, Nara Women's University, Nara, 630-8506, Japan*

† Electronic supplementary information (ESI) available. CCDC reference numbers 801460, 801461, 807172, 807173, 813345 and 813714. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ce05155e

‡ Present address of T. Echigo: *Environment and Energy Materials Research Division, National Institute for Materials Science, 1-1 Namiki, Tsukuba, Ibaraki 305-0044, Japan*

View Online

Published on 21 April 2011 on http://pubs.rsc.org | doi:10.1039/C1CE05155E
Downloaded on 18 May 2011

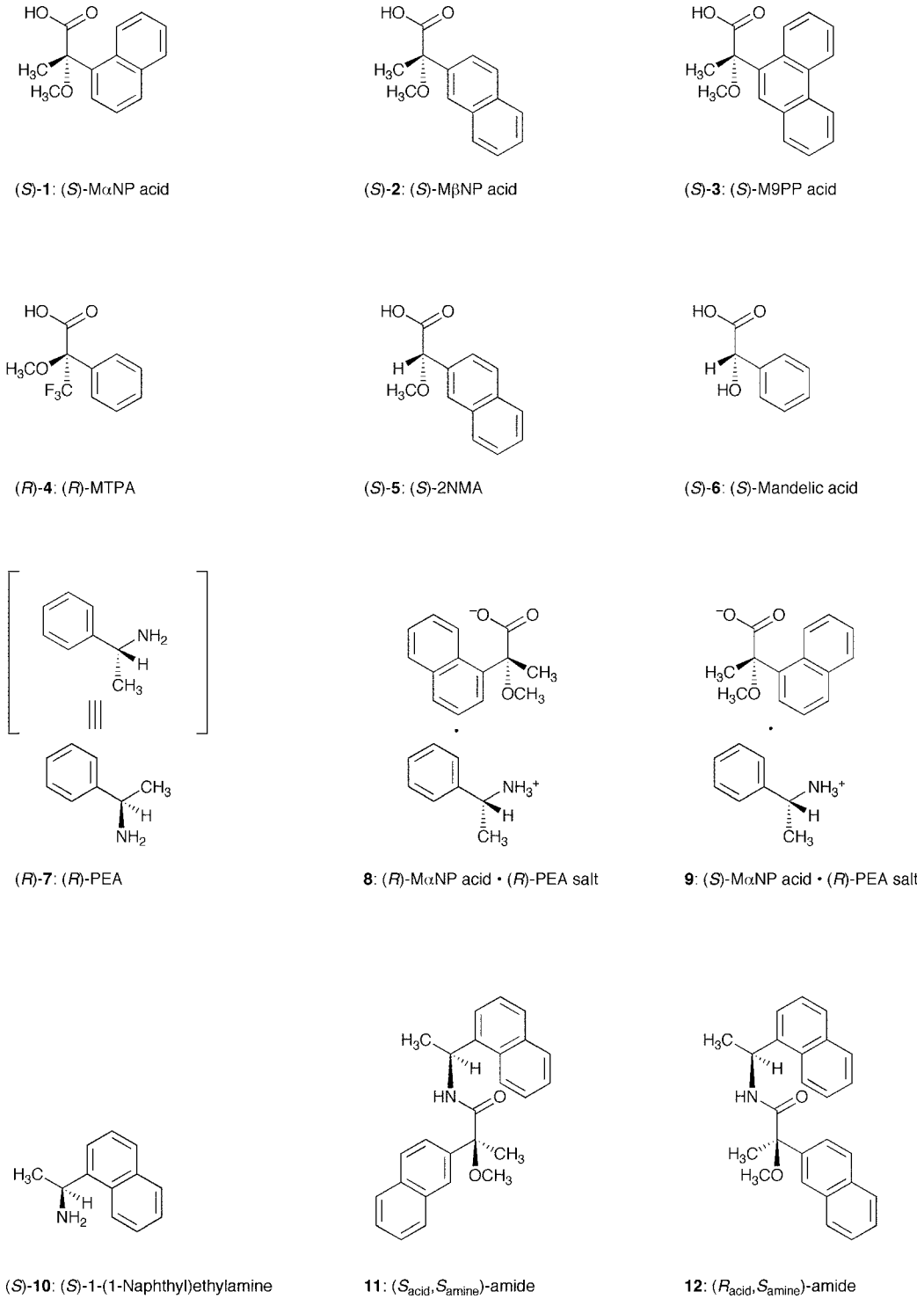


Fig. 1 Structures of chiral resolving agents and their derivatives.

formed a chain-like motif called a catemer.[14] A similar structure was observed in crystalline (*S*)-**1**.[9]

The crystalline conformation of the (*S*)-MαNP ester was similar to those of acids (*S*)-**1** and (*S*)-**3** as follows (Fig. 2).[3,9–11] The methine group of the alcohol moiety and the carbonyl group were *syn*. The carbonyl and methoxy groups were also *syn*, forming the MαNP plane, and the methyl group and the aromatic hydrogen atom at the 2-position were *syn*. ^{1}H NMR analyses suggested that this conformation was also predominant when the compounds were dissolved in chloroform-*d*. Large high-field shifts were observed at the alcohol substituent R_1. The more polar diastereomeric MαNP ester, in which the larger and more hydrophobic substituent overlapped the 1-naphthyl group, yielded crystals.[10]

X-Ray crystallographic data and NMR spectra of the (*R*)-MαNP amide[3,11] suggested that the methine group of the amine

 This journal is © The Royal Society of Chemistry 2011

View Online

Published on 21 April 2011 on http://pubs.rsc.org | doi:10.1039/C1CE05155E
Downloaded on 18 May 2011

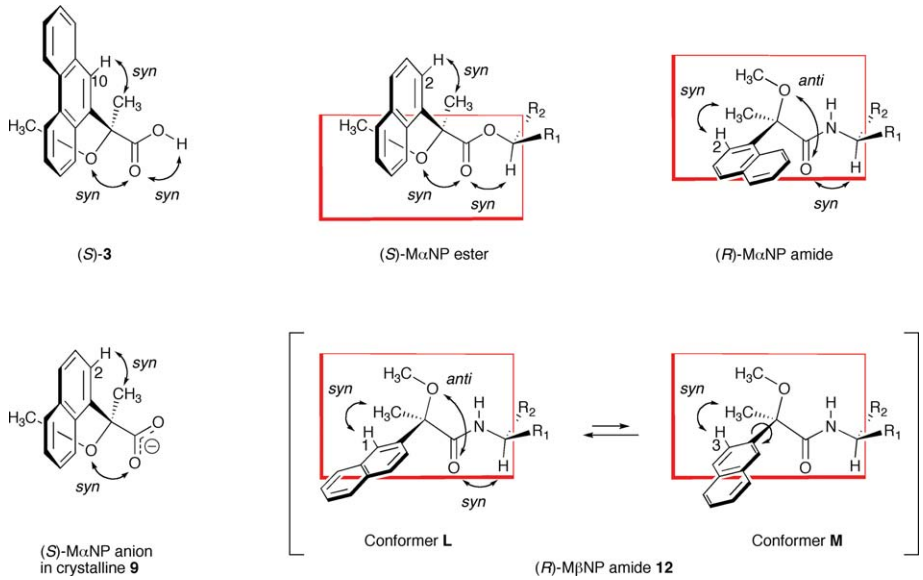


Fig. 2 Conformations of 2-aryl-2-methoxypropanoic acid and derivatives.

moiety and the carbonyl group were *syn*, while the carbonyl and the methoxy groups were *anti* (Fig. 2). In addition, the methyl group of the MαNP moiety and the aromatic hydrogen atom at the 2-position were *syn*. Smaller or even irregular $\Delta\delta$ values were observed in the ^{1}H NMR spectra of the MαNP amides.[11]

In 1978, Goto *et al.* synthesised (*R*)-**1** and (*R*)-**2** with (*R*)-**7** *via* diastereomeric salt formation, and applied them to the enantioresolution of amino acid methyl esters.[15] Nevertheless, the crystal structures of the MαNP and MβNP salts and the chiral recognition mechanisms of the crystals have yet to be clarified.

Diastereomeric salt formation is a metal-free process that also serves to remove contaminants.[16] More than half of all chiral pharmaceuticals have been estimated to be produced by the crystallisation of diastereomeric salts.[17] Saigo elucidated a chiral recognition mechanism during preferential and diastereomeric crystallisations and applied the process to the preparation of enantiopure compounds.[18,19] Several natural and synthetic acids have been used as chiral resolving agents in the enantioresolution of amines by forming the diastereomeric salts.[20] Among them, mandelic acid **6** is one of the most important chiral resolving agents.[16,20,21]

Acids **1–3** possess non-racemisable chiral centres and relatively large aromatic groups. These properties make them useful for large-scale preparations of single-enantiomer biofunctional molecules, agrochemicals, and pharmaceuticals using the diastereomeric salt formation method. For this reason, the elucidation of chiral recognition mechanisms is important for the crystal engineering[12–14] of diasteremeric salts prepared from acids **1–3**.

In both the crystalline MαNP salts [*i.e.*, the less-soluble diastereomeric salt **8**, prepared from (*R*)-**1** and (*R*)-**7**;[15] and the more-soluble diastereomeric salt **9**, prepared from (*S*)-**1** and (*R*)-**7**], the conformation of the MαNP anion was similar to those of MαNP acid and its esters as follows (Fig. 2). The three oxygen atoms of the caboxylato (–COO$^-$) and methoxy groups were almost in the MαNP plane, and the methyl group and the aromatic hydrogen atom at the 2-position were *syn*, indicating the strict conformational requirement of 1-naphthyl group.

The less-soluble diastereomeric salt **8** formed an ammonium–carboxylate ion pair by a methoxy-assisted salt bridge and an aromatic CH$\cdots\pi$ interaction[22–25] acting as supramolecular synthons[22] [Fig. 3 and 4 (A)]. The MαNP anion and the ammonium ion acted as a proton acceptor and donor (or electron donor and acceptor), respectively.[26] A methoxy-assisted salt bridge was also observed in salt **9**. However, the naphthyl and phenyl groups of the ion pair did not overlap [Fig. 4 (B)]. Instead, salt **9** formed another ammonium–carboxylate ion pair by means of a normal salt bridge, a CH$\cdots$O hydrogen bond, and a $\pi\cdots\pi$ interaction [Fig. 4 (C)].

The crystal packing of salts **8** and **9** was also investigated with regard to the weak interactions (*i.e.*, salt bridges, NH$\cdots$O and CH$\cdots$O hydrogen bonds, and aromatic CH$\cdots\pi$, CH$\cdots\pi$, and $\pi\cdots\pi$ interactions).[27–29] The identification of these weak intermolecular interactions in the crystals will be useful in understanding ligand–receptor interactions in biofunctional molecules and can be used toward the rational design of agrochemicals and pharmaceuticals.

Unlike acids **1** and **3**, many of the analytical properties of acid **2**[3,15,30,31] have not been characterised. For this reason, solution-phase structures of diastereomeric MβNP amides **11** and **12** were determined by two-dimensional NMR analyses. The 2-naphthyl group of acid **2** was stereochemically less demanding and longer

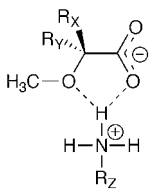


Fig. 3 Methoxy-assisted salt bridge as a supramolecular synthon.

View Online

Published on 21 April 2011 on http://pubs.rsc.org | doi:10.1039/C1CE05155E
Downloaded on 18 May 2011

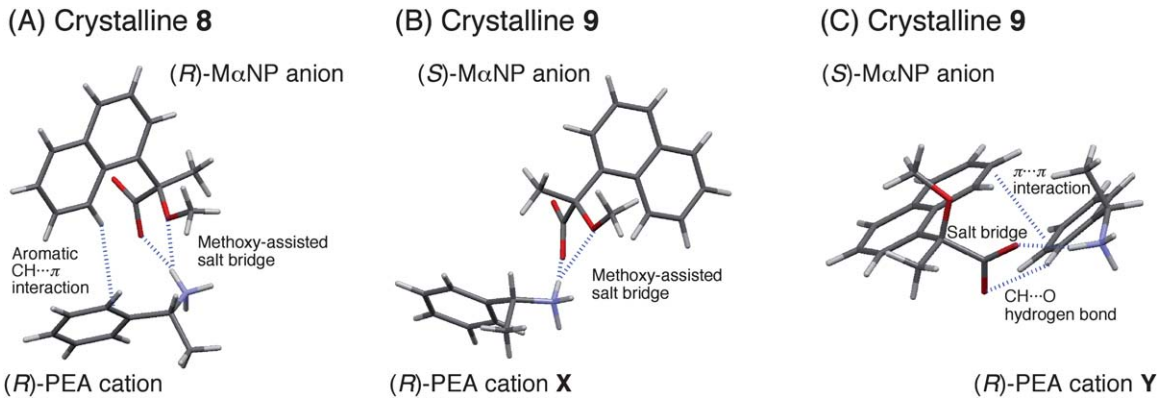


Fig. 4 Chiral recognitions in salts **8** and **9**.

than the 1-naphthyl group of acid **1**. Therefore, the conformation of the MβNP moiety was more flexible than the MαNP moiety (Fig. 2): the methyl group was *syn* to the aromatic hydrogen atoms at the 1- and 3-positions of the conformers **L** and **M**, respectively. In addition, MβNP amides **11** and **12** were less polar than the corresponding MαNP amides,[11] and yielded a higher-resolution separation in normal-phase HPLC.[3] The ^{1}H NMR anisotropy method, which can be used to assign relative stereochemistry, was applied to amides **11** and **12**.

Results and discussion

Crystal conformation of the less-soluble diastereomeric salt 8

Salt **8**[15] was prepared from (*R*)-**1** and (*R*)-**7** and was recrystallised from a mixture of methanol and chloroform. Table 1 and Fig. 5 show the crystallographic data and the ORTEP drawing of salt **8**. Salt **8** crystallised in the monoclinic space group $P2_1$ with two sets of molecules in a unit cell.

Table 1 X-Ray crystallographic data for salts **8** and **9**

Compound	**8**	**9**
Molecular formula	$C_{22}H_{25}NO_3$	$C_{22}H_{25}NO_3$
Formula weight	351.44	351.44
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$
Z	2	2
a/Å	11.3857(9)	9.3455(7)
b/Å	6.7698(3)	6.7383(4)
c/Å	12.7237(9)	14.6868(12)
β/°	103.730(4)	101.529(4)
V/Å^3	952.70(11)	906.21(12)
$D_{calculated}$	1.225	1.288
μ/cm^{-1}	0.809	0.850
$2\theta_{max}$/°	55.0	55.0
Temperature/K	123	123
No. of reflections collected	7339	7051
No. of reflections unique	4296	4082
R_{int}	0.014	0.022
No. of parameters	336	336
Final $R1$ ($I > 2\theta(I)$)[a]	0.0403	0.0494
wR_2 (all data)[b]	0.0991	0.1220
GOF	1.130	1.089
Flack parameter	−0.4(10)	−0.3(13)

[a] $R1 = (\Sigma||F_o| - |F_c||)/(\Sigma|F_o|)$. [b] $wR2 = \{[\Sigma w(F_o^2 - F_c^2)^2]/[\Sigma w(F_o^2)^2]\}^{1/2}$.

The conformation of the (*R*)-MαNP anion was similar to those of (*R*)-**1** and the (*R*)-MαNP ester. Table 2 shows the dihedral angles, interatomic distances, and interatomic angles of salt **8**. The three oxygen atoms of the carboxylato and methoxy groups were almost in the MαNP plane. The dihedral angles O1–C1–C2–O3 and C4–O3–C2–C1 were −27.17(19)° and +177.82(14)°, respectively. The methyl group was in the aromatic plane with the dihedral angle C3–C2–C5–C6 = −0.1(2)°. As already reported for the MαNP esters,[9,10] short distances were observed between the aromatic hydrogen atom H13 and the carboxylate oxygen atom O1 [d_1 = 2.875(19) Å], and between H13 and the methoxy oxygen atom O3 [d_2 = 2.43(3) Å].[33] For this reason, the ammonium group was slightly offset from the MαNP plane [Fig. 4 (A)]. The same was true for salt **9** [Fig. 4 (B)]. In the PEA cation, the dihedral angle C16–C15–C17–C18 was −66.64(19)°. Recently, He *et al.* reported the crystal structures of diastereomeric salts prepared from chlorine-substituted mandelic acid and (*R*)-**7**.[32]

Desiraju introduced the concept of supramolecular synthons,[22] which are the common spatial arrangements of intermolecular interactions in crystals. In crystalline salt **8**, the ammonium–carboxylate ion pair was formed by supramolecular synthons

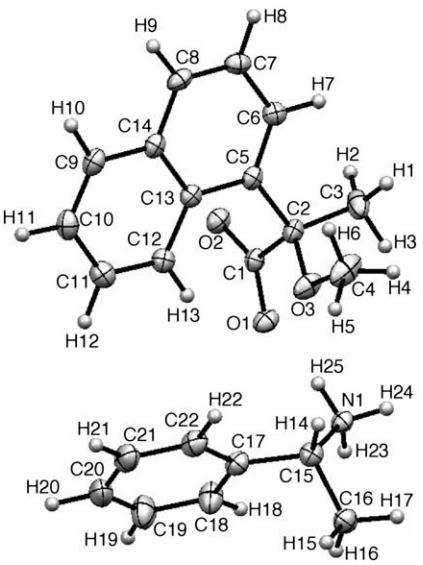


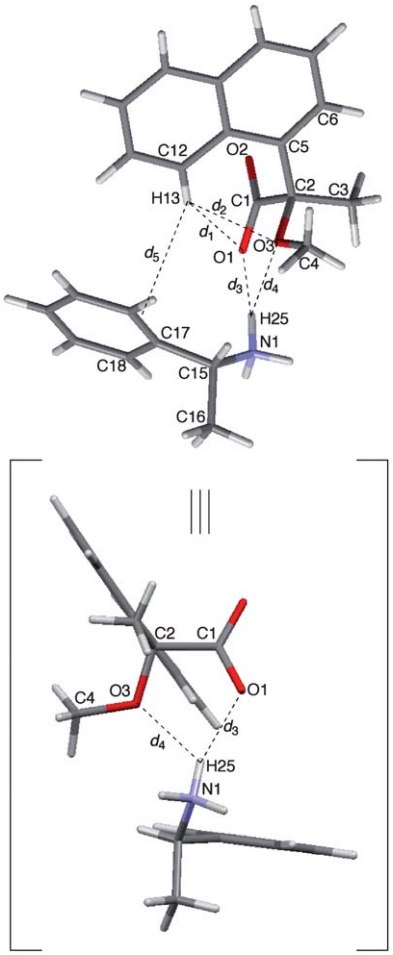
Fig. 5 ORTEP drawing of salt **8**.

This journal is © The Royal Society of Chemistry 2011

View Online

Published on 21 April 2011 on http://pubs.rsc.org | doi:10.1039/C1CE05155E
Downloaded on 18 May 2011

Table 2 Dihedral angles, interatomic distances, and interatomic angles of crystalline **8**[a]



8: (*R*)-MαNP acid•(*R*)-PEA salt

Dihedral angle (°)	
O1–C1–C2–O3	−27.17(19)
C4–O3–C2–C1	+177.82(14)
C3–C2–C5–C6	−0.1(2)
C16–C15–C17–C18	−66.64(19)
Interatomic distance (Å)	
H13···O1 (= d_1)	2.875(19)
H13···O3 (= d_2)	2.43(3)
H25···O1 (= d_3)	2.02(3)
H25···O3 (= d_4)	2.30(3)
H13···π (= d_5)	3.15(2)
Interatomic angle (°)	
C12–H13···O1	142.0(17)
C12–H13···O3	116.5(16)
N1–H25···O1	161(2)
N1–H25···O3	125.1(19)

[a] The van der Waals radii (Å): C, 1.70; H, 1.20; O, 1.52; the half-thickness of aromatic ring, 1.77.

consisting of a methoxy-assisted salt bridge[26] (Fig. 3) and an aromatic CH···π interaction.[28,29] As shown in Table 2, the interatomic distances between the ammonium hydrogen atom H25 and the carboxylate oxygen atom O1 [d_3 = 2.02(3) Å] and between H25 and the methoxy oxygen atom O3 [d_4 = 2.30(3) Å] were relatively short.[26,33] The multipoint recognition of functional groups is expected to improve synthon robustness.[22] Similar bifurcated hydrogen bonds have been observed in crystalline (*S*)-**1**, (*RS*)-**1** and (*S*)-**3**.[9,11] The aromatic hydrogen atom H13 of the naphthyl group was almost above the neighbouring phenyl plane [d_5 = 3.15(2) Å]. This distance suggests contribution of an aromatic CH···π interaction.[29,33]

Kobayashi and Saigo reported that the characteristics of aromatic CH···π interactions in bulk crystals resemble a conventional hydrogen bond with regard to co-operativity, the polarisation of the bond, and the shortened interaction distance.[19] Recently, Headen *et al.* considered the π···π interactions in aromatic liquids. They found that neighbouring aromatic rings are predominantly perpendicular when the distance between their centres is large (>5 Å) and that two H atoms per molecule are directed toward the acceptor's π orbitals in a Y-shaped configuration.[23] They further reported a preference for parallel π···π contacts at smaller molecular separations (<5 Å).[23]

Sakai *et al.* introduced the concept of a space filler.[16] They found that the diastereomeric salt formation method was most successful when the chiral resolving agent and the racemic substrate had the same molecular length (*i.e.*, the same number of bonds between the most distant carbon atom and the carboxy or amino groups). Considering the role of the methoxy group, the MαNP anion was five bond lengths from the MαNP plane. The identical distance was observed in the PEA cation [Fig. 4 (A)]. For this reason, salt **8** crystallised without any space fillers such as water or methanol.

As discussed above, the methoxy-assisted salt bridge and aromatic CH···π interactions play an important role in the chiral recognition of crystalline salt **8**.

Crystal packing of the less-soluble diastereomeric salt 8

Fig. 6 (A) shows the crystal packing of salt **8** as viewed along the *a*-axis. Fig. 6 (B) displays the homoaromatic CH···π interactions. The distances between H10 and H11 of the naphthyl group and the neighbouring naphthyl group were 2.4 Å and 3.1 Å, respectively. Similar relationships were observed in the PEA anions in which the distance between H21 of the phenyl group and the neighbouring phenyl group was 3.3 Å [Fig. 6 (C)]. Tsuzuki *et al.* reported that the major source of attraction in benzene dimers is long-range interactions.[25] However, the distances observed here suggest that CH···π interactions between phenyl groups were weaker than those between naphthyl groups.[33]

In addition, the methoxy group of the MαNP anion, and the methyl group of the PEA cation, helped stabilise the crystal structure through intermolecular CH···π interactions. The distances between H4 and H5 of the methoxy group and the neighbouring naphthyl group were 2.9 Å and 2.7 Å, respectively [Fig. 6 (B)], while the distance between H15 of the methyl group and the phenyl group of the neighbouring PEA cation was 3.0 Å [Fig. 6 (C)]. Note that the methoxy group allows stacking of the MαNP anions by acting as an internal space filler.

Fig. 6 (D) shows that salt **6** forms a polar column[19,32] facilitated by salt bridges and hydrogen bonds (*i.e.*, NH···O–CH_3)

View Online

Published on 21 April 2011 on http://pubs.rsc.org | doi:10.1039/C1CE05155E
Downloaded on 18 May 2011

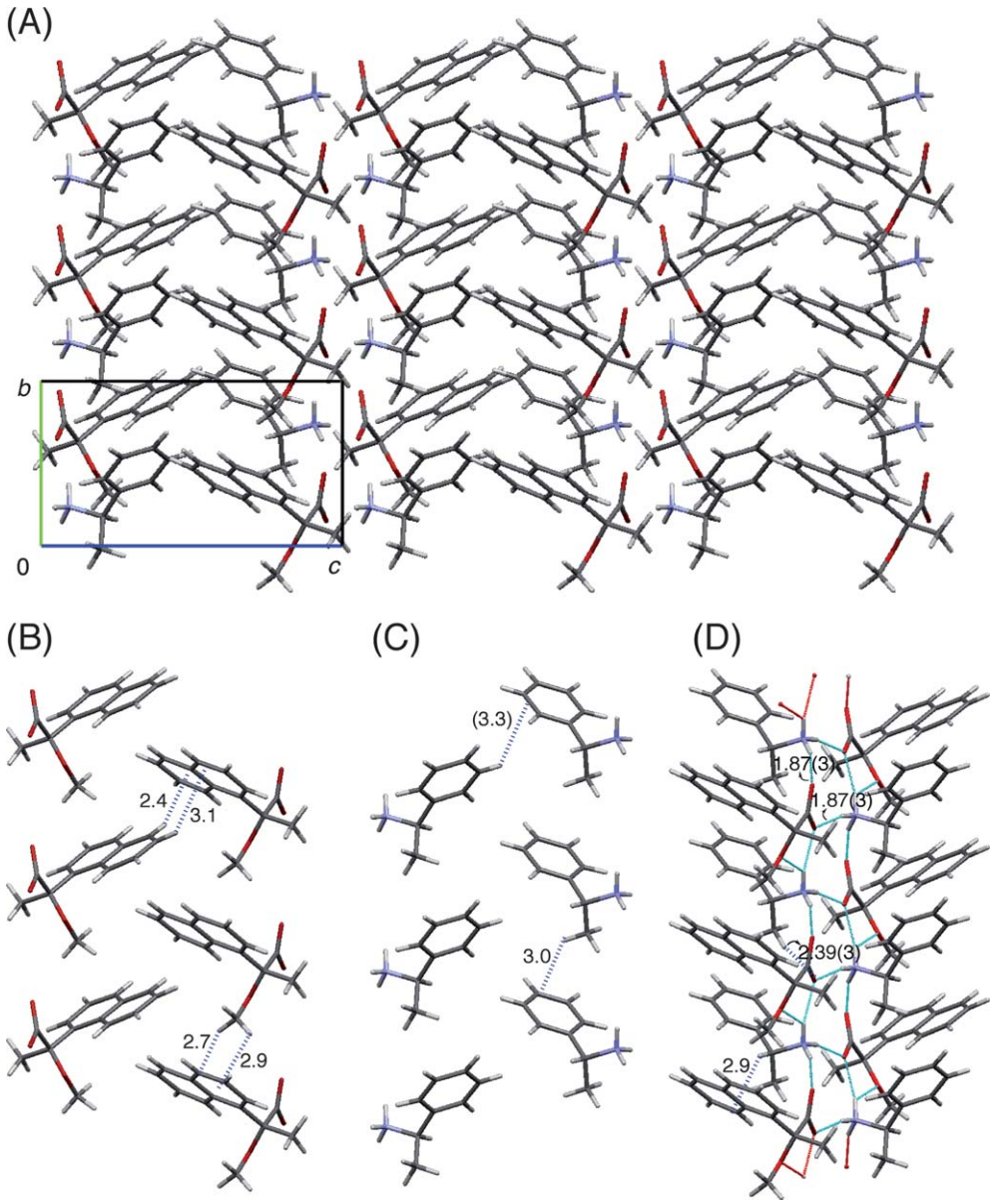


Fig. 6 The crystal packing of salt **8** as viewed along the *a*-axis. The assigned numbers are distances between atoms or moieties (Å).

that act as supramolecular cement.[26] In addition to the methoxy-assisted salt bridge (see above), conventional salt bridges were observed between the ammonium and carboxylato groups: both the interatomic distances between H23/O1 and H24/O2 were 1.87 (3) Å. A CH···O interaction was observed between H17, the hydrogen atom in the methyl group of PEA cation and the neighbouring carboxylate oxygen atom O1 at a distance of 2.39 (3) Å. Furthermore, a CH···π interaction was observed between H14, the hydrogen atom attached to the chiral centre of PEA cation and the neighbouring naphthyl group at a distance of 2.9 Å.

A herringbone motif was again observed in the crystal packing when viewed along the *c*-axis (Fig. 7). Although the aromatic hydrogen atoms were not located closely above the aromatic moieties, the short contacts were observed in addition to those noted above: the distances between H12/C21 and H19/C6 were 2.88(3) Å and 2.85(3) Å, respectively. It is probable that these heteroaromatic CH···π interactions between the naphthyl and phenyl groups contributed to the crystal packing of salt **8**.

Crystal conformation of the more-soluble diastereomeric salt 9

Salt **9** was prepared from (*S*)-**1** and (*R*)-**7** and was recrystallised from a mixture of methanol and chloroform. Table 1 and Fig. 8 show the crystallographic data and the ORTEP drawing of salt **9**, respectively. Salt **9** crystallised in the monoclinic space group $P2_1$ with two sets of molecules in a unit cell. This is the first preparation of the more-soluble diastereomeric salt **9**.

The dihedral angles, interatomic distances, and interatomic angles of salt **9** are shown in Table 3. The carboxylato and methoxy groups of salt **9** were in the MαNP plane: the dihedral angles O1–C1–C2–O3 and C4–O3–C2–C1 were +16.3(3)° and

 This journal is © The Royal Society of Chemistry 2011

View Online

Published on 21 April 2011 on http://pubs.rsc.org | doi:10.1039/C1CE05155E
Downloaded on 18 May 2011

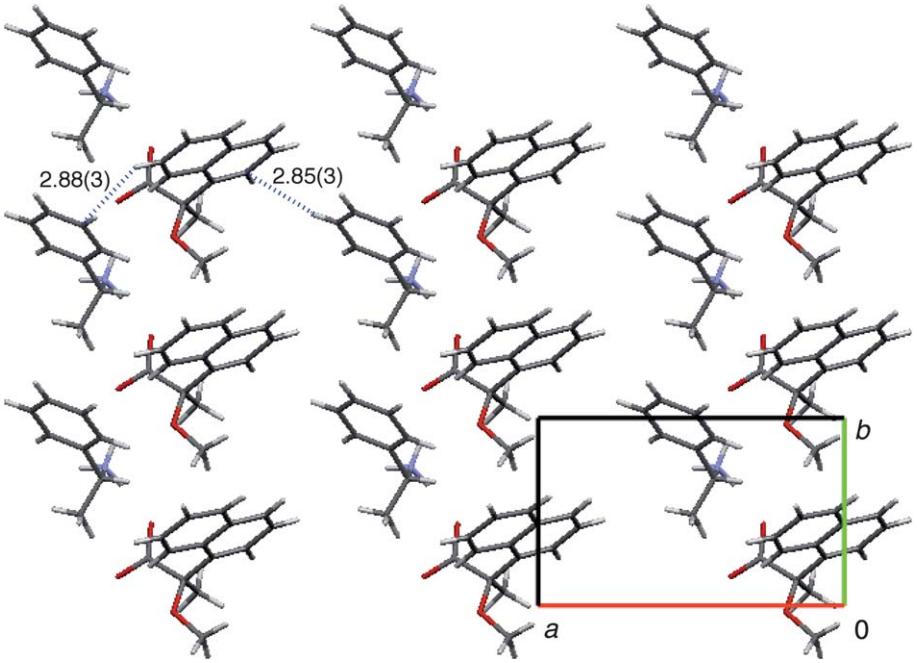


Fig. 7 Crystal packing of salt **8** as viewed along the *c*-axis. The assigned numbers are distances between atoms (Å).

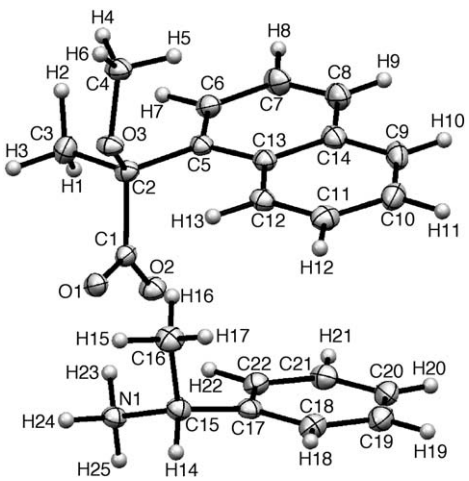


Fig. 8 ORTEP drawing of salt **9**.

+171.24(17)°, respectively. The methyl group was in the aromatic plane with dihedral angle C3–C2–C5–C6 = −0.5(3)°. The aromatic hydrogen atom H13 of the naphthyl group formed a bifurcated CH···O hydrogen bond[9] with d_1 = 2.66(3) Å and d_2 = 2.40(3) Å. In the PEA cation, the dihedral angle C16–C15–C17–C22 was −92.2(3)°.

A methoxy-assisted salt bridge was also observed in salt **9** (Table 3). The interatomic distances d_3 and d_4 between H25′ of the PEA cation **X** and oxygen atoms O1 and O3 of the MαNP anion were 1.87(4) Å and 2.38(4) Å, respectively. However, the 1-naphthyl group and the phenyl group of PEA cation **X** did not overlap [Fig. 4 (B) and Table 3].

Instead, the MαNP anion formed a close ion pair with PEA cation **Y** [Fig. 4 (C) and Table 3]. The interatomic distance d_5 between H23 of the ammonium group and O1 of the carboxylato group was 1.81(3) Å, suggesting a salt bridge.[26] In addition, a CH···O hydrogen bond was observed: the interatomic distance d_6 between the aromatic hydrogen atom H22 and O2 of the carboxylato group was 2.44(3) Å. Furthermore, the naphthyl and phenyl groups were nearly parallel and slightly overlapping, suggesting a π···π interaction: the interatomic distance d_7 between the aromatic carbon atoms C11 and C21 was 3.327(4) Å. This distance was shorter than the sum of the half-thickness of the phenyl groups and almost identical to the distance between parallel base pairs in double-stranded DNA.[34] However, the partial overlap of aromatic groups suggests limited contributions from π···π interactions.[24] The parallel pairs of aromatic groups form a motif similar to a sandwich herringbone (see below). Desiraju and Gavezzotti reported an important predictive mapping for the crystal structures of polynuclear aromatic hydrocarbons based on the glide-to-stack ratio as a function of the total molecular surface.[13]

Recently, we reported the crystal structure of a diastereomeric amide prepared from (*R*)-**1** and (*S*)-**10**.[11] Similar to crystalline salt **9**, which was prepared from (*S*)-**1** and (*R*)-**7**, the two naphthyl groups of the (R_{acid},S_{amine})-MαNP amide were almost parallel and formed a herringbone motif. To fill the space, the benzyl moiety of the PEA cation **Y** overlapped with the naphthyl group of the MαNP cation in salt **9** [Fig. 4 (C) and Table 3]. Note that the parallel pairs of aromatic groups formed the herringbone motif with other aromatic groups in both the crystalline MαNP amide and its corresponding salt.

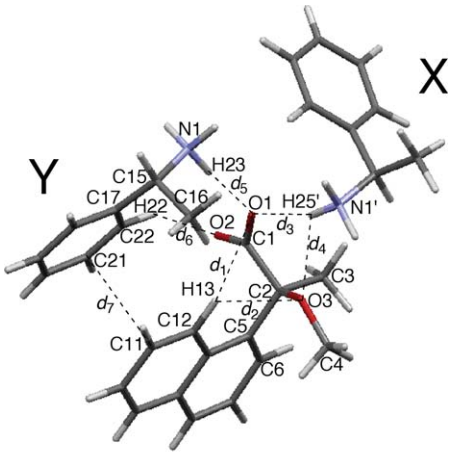
Crystal packing of the more-soluble diastereomeric salt 9

Fig. 9 (A) shows the crystal packing of salt **9** as viewed along the *a*-axis. Aromatic CH···π interactions between naphthyl groups resulted in a motif similar to a sandwich herringbone.[12] The distance between aromatic hydrogen atoms H10 and the naphthyl

View Online

Published on 21 April 2011 on http://pubs.rsc.org | doi:10.1039/C1CE05155E
Downloaded on 18 May 2011

Table 3 Dihedral angles, interatomic distances, and interatomic angles of crystalline **9**[a]



9: (*S*)-MαNP acid•(*R*)-PEA salt

Dihedral angle (°)	
O1–C1–C2–O3	+16.3(3)
C4–O3–C2–C1	+171.24(17)
C3–C2 –C5–C6	−0.5(3)
C16–C15–C17–C22	−92.2(3)
Interatomic distance (Å)	
H13···O1 (= d_1)	2.66(3)
H13···O3 (= d_2)	2.40(3)
H25′···O1 (= d_3)	1.87(4)
H25′···O3 (= d_4)	2.38(4)
H23···O1 (= d_5)	1.81(3)
H22···O2 (= d_6)	2.44(3)
C11···C21 (= d_7)	3.327(4)
Interatomic angle (°)	
C12–H13···O1	134.3(19)
C12–H13···O3	114.4(16)
N1′–H25′···O1	162(3)
N1′–H25′···O3	124(3)
N1–H23···O1	167(3)
C22–H22···O2	148(3)

[a] The van der Waals radii (Å): C, 1.70; H, 1.20; O, 1.52; the half-thickness of aromatic ring, 1.77.

group of the neighbouring MαNP anion was 2.5 Å [Fig. 9 (B)]. Considering the distance between the phenyl groups as defined by the distance between aromatic hydrogen atom H18 and the neighbouring phenyl plane (3.9 Å), aromatic CH···π interactions between phenyl groups were not significant [Fig. 9 (C)].

As noted above, the methoxy group of the MαNP anion and the methyl group of the PEA cation helped stabilise the crystal structure through CH···π interactions. The distance between H6 of the methoxy group and the naphthyl group of the neighbouring MαNP anion was 2.8 Å. The distances between H15 and H17 of the methyl group and the neighbouring phenyl group were 3.2 Å and 3.1 Å, respectively. In addition, CH···O interactions were observed between MαNP anions. The interatomic distance between H6 of the methoxy group and O2 of the neighbouring MαNP anion was 2.59(3) Å [Fig. 9 (B)]. CH···O interactions were also observed between H15 of the methyl group of the PEA cation and O2 of the neighbouring MαNP anion at a distance of 2.59(3) Å [Fig. 9 (D)].

Salt bridges and conventional hydrogen bonds (*i.e.*, NH···O–CH_3) formed a polar layer. In addition to the interactions shown in Table 3, a salt bridge was formed between the O2 of the carboxylato group and H24 of the neighbouring ammonium group with an interatomic distance of 1.89(4) Å [Fig. 9 (D)].

As viewed along the *c*-axis, the methyl group of the MαNP anion was close to the phenyl group (Fig. 10). The interatomic distance between H1 of the methyl group and C18 of the neighbouring phenyl group was 2.72(4) Å. However, neither aromatic CH···π interactions nor CH···O hydrogen bonds were observed between the sandwich herringbone structures.

The considerable contributions of the methoxy-assisted salt bridge and larger aromatic groups to chiral recognition imply that diastereomeric salt formation employing (*S*)- or (*R*)-2-aryl-2-methoxypropanoic acids will be important in the preparation of single-enantiomer biofunctional molecules, agrochemicals, and pharmaceuticals.

NMR analyses of MβNP amides 11 and 12

Acids **1** and **3** exhibited similar analytical properties in normal-phase HPLC separations of their diastereomeric esters and in the ^{1}H NMR anisotropy measurements.[6] However, many of the analytical properties of acid **2** have yet to be characterised.[3,30,31]

To investigate these properties, (*RS*)-**2** was condensed with (*S*)-**10** to yield the diastereomeric amides **11** and **12**. Amide **11** was also prepared from (*S*)-**2**[31] and (*S*)-**10**. Therefore, the stereochemistry was assigned as (S_{acid},S_{amine})-**11** and (R_{acid}, S_{amine})-**12**, respectively. The NMR signals of amides **11** and **12** were assigned based on the analyses of the two-dimensional NMR spectra consisting of DQF COSY, NOESY, HMQC, and HMBC measurements at 800 MHz in chloroform-*d*. This report constitutes the second NMR analysis of the MβNP amides. Previously, we reported the NMR data of the MβNP amides prepared from phenylglycine methyl ester (PGME).[30]

As discussed for the MαNP amides prepared from (*S*)-**10**,[11] a coupling constant of 8.5 Hz was observed for the amide proton (δ 7.25) in the ^{1}H NMR spectra of amide **11** (Fig. 11). This suggests that the amide hydrogen atom and the vicinal hydrogen atom at the 15-position (δ 5.90) adopted a *trans* conformation in solution. Recently, Takahashi *et al.* reported that the CH···O hydrogen bond contributes to the stabilization of the CH_3/C=O eclipsed or *gauche* conformation of methyl formate, *N*-methylformamide and propanal.[29] Steiner and Saenger discussed the origin of similar five-membered circular arrangements.[35] Considering the NH···O hydrogen bond between the amide NH and methoxy group,[11,30] it is probable that the carbonyl and methoxy groups adopted an *anti* conformation (Fig. 2). Similar relationships were observed for amide **12**. The high-field shifts observed for the protons at the 23- and 24-positions (δ 7.16 and δ 7.78, respectively) in amide **12** suggest shielding by the 2-naphthyl group.

The NOESY spectra of amides **11** and **12** showed major and minor crosspeaks between the methyl group of MβNP moiety and the aromatic hydrogen atoms at the 1- and 3-positions of the 2-naphthyl groups, respectively (Fig. 2 and 11). This result suggests the higher rotational freedom of the 2-naphthyl group than the 1-naphthyl group.[36] Harada *et al.* observed the conformer **L** of MβNP amide by X-ray crystallography, in which

 This journal is © The Royal Society of Chemistry 2011

View Online

Published on 21 April 2011 on http://pubs.rsc.org | doi:10.1039/C1CE05155E
Downloaded on 18 May 2011

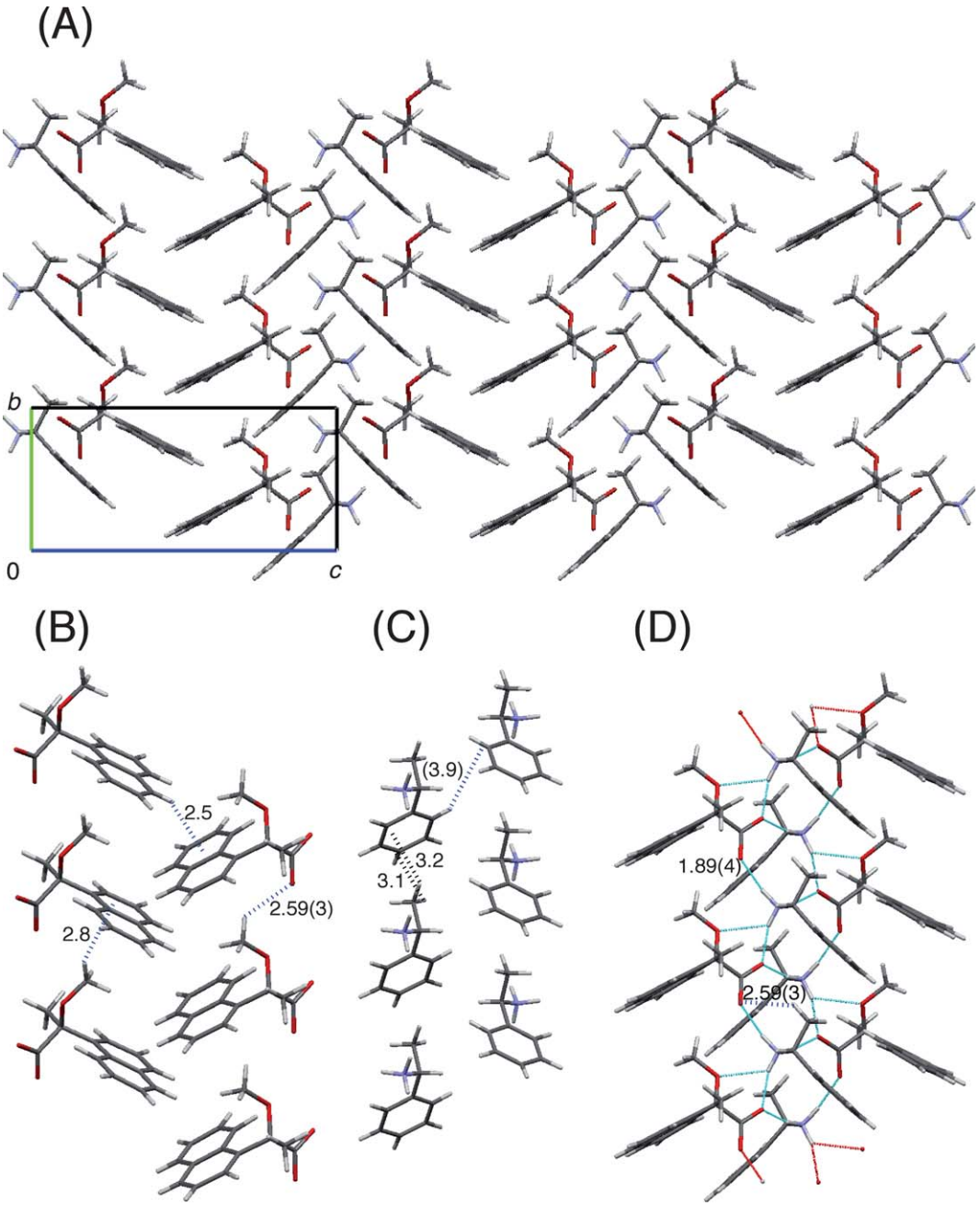


Fig. 9 Crystal packing of salt **9** as viewed along the *a*-axis. The assigned numbers are distances between atoms or moieties (Å). The partially extracted figures (B) and (C) were rotated to clarify the intermolecular interactions.

the methyl group and the aromatic hydrogen atom at the 1-position were *syn*.[3]

The $\Delta\delta$ values of the ^{1}H NMR spectra suggest that the two naphthyl groups of amide **12** were parallel and shielded each other (Fig. 11). These data also suggest that NMR analyses of the MβNP amides could be used for the elucidation of the relative stereochemistry as a supplement to X-ray crystallography.

Chromatographic analysis of MβNP amides 11 and 12

The separation of amides **11** and **12** was investigated on a normal-phase HPLC column (silica SG80, 250 × 4.6 mm I.D.; eluent, hexane–ethyl acetate = 4 : 1, 0.5 mL min^{-1}; detection, UV absorbance at 280 nm). Fig. 12 shows that the retention times of amides **11** and **12** were 12.91 and 21.37 min, respectively. Similar to the MαNP ester and amide, the MβNP amide **12**, which possesses a larger and more hydrophobic substituent of the amine moiety that overlaps the aromatic group of the acyl moiety, was more polar.[10,11] The separation factor (α) and resolution (*R*s) for amides **11** and **12** were 2.25 and 18.0, respectively. The separation efficiency of the MβNP amides was better than those for the MαNP amides (α = 2.03, *R*s = 17.4) prepared from (*S*)- and (*R*)-**1** with (*R*)-**10** under identical conditions.[3,11]

Note that the retention times of the MβNP amides **11** and **12** (see above) were shorter than those of the corresponding MαNP

View Online

Published on 21 April 2011 on http://pubs.rsc.org | doi:10.1039/C1CE05155E
Downloaded on 18 May 2011

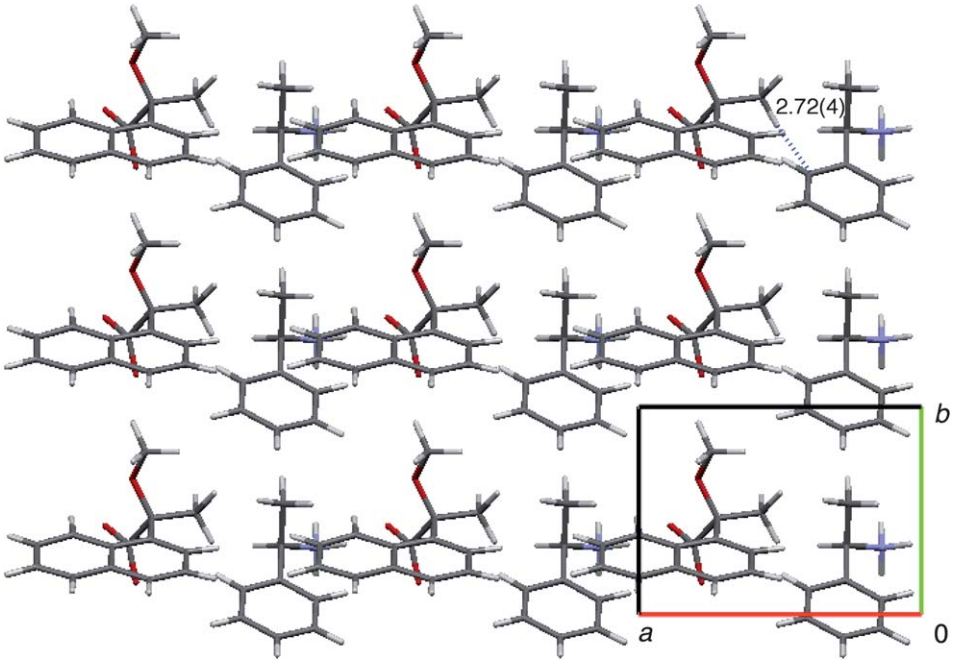


Fig. 10 Crystal packing of salt **9** as viewed along the *c*-axis. The assigned number is interatomic distance between atoms (Å).

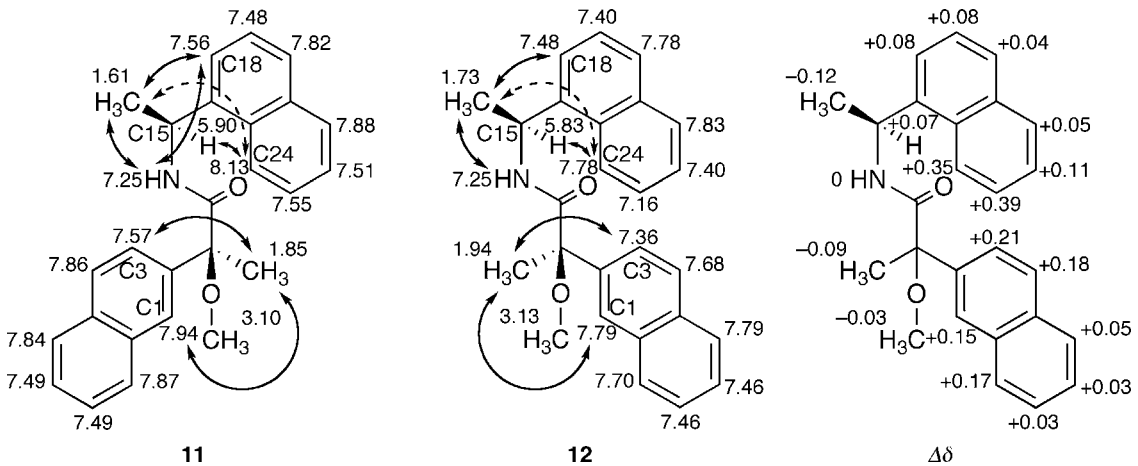


Fig. 11 The ^{1}H NMR chemical shifts and $\Delta\delta$ values for amides **11** and **12**. $\Delta\delta = \delta$[(*S*)-MβNP amide] − δ[(*R*)-MβNP amide] = δ(amide **11**) − δ(amide **12**). Solid arrows indicate NOESY correlations, whereas dashed arrows indicate weak ones.

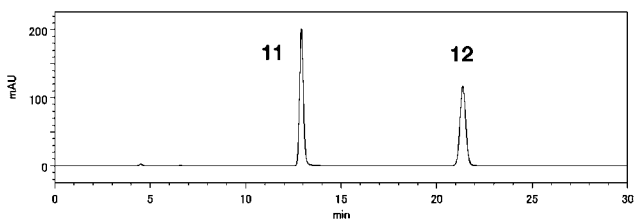


Fig. 12 HPLC profiles for MβNP amides **11** and **12**. Analyte, amides **11** and **12**, each 1 μg in 2μL of ethanol; column, silica SG80 (250 mm × 4.6 mm I.D.); eluent, hexane–ethyl acetate = 4 : 1, 0.5 mL min^{-1}; detection, UV absorbance at 280 nm. Retention time, t_0 (1,3,5-tri-*tert*-butylbenzene) = 6.16 (min), t_1 = 12.91, t_2 = 21.37; peak width, W_1 = 0.37 (min), W_2 = 0.57; α (separation factor) = 2.25; *R*s (resolution) = 18.0. $\alpha = (t_2 - t_0)/(t_1 - t_0)$; $Rs = 2 \times (t_2 - t_1)/(W_1 + W_2)$.

amides.[11] The less-polar MαNP amide prepared from (*S*)-**1** and (*S*)-**10** exhibited a retention time of 15.62 min, while the more-polar MαNP amide prepared (*R*)-**1** and (*S*)-**10** had a retention time of 25.37 min. The 2-naphthyl group of acid **2** is longer than the 1-naphthyl group of acid **1**. These differences in polarity and molecular length will be important in the crystal engineering of their derivatives.

Conclusions

The crystal structures of diastereomeric salts prepared from (*R*)- and (*S*)-**1** with (*R*)-**7** were first elucidated by X-ray crystallography. The conformation of the MαNP anion was similar to those of the MαNP acid and its esters. The three oxygen atoms of

 This journal is © The Royal Society of Chemistry 2011

View Online

Published on 21 April 2011 on http://pubs.rsc.org | doi:10.1039/C1CE05155E
Downloaded on 18 May 2011

the carboxylato and methoxy groups were nearly in the MαNP plane, and the methyl group was *syn* to the aromatic hydrogen atom at the 2-position. These crystal structures contained a methoxy-assisted salt bridge acting as a supramolecular synthon. The bifurcated structure of this synthon implies robust structure.

In the less-soluble diastereomeric salt **8**, the (*R*)-MαNP and (*R*)-PEA ions formed a close ion pair through a methoxy-assisted salt bridge and an aromatic CH···π interaction. The molecular length of the (*R*)-MαNP and (*R*)-PEA ions from the MαNP plane were well matched, suggesting that the distance from the MαNP plane is critical to crystal engineering in this class of molecules. The salt bridges, NH···O hydrogen bond, and CH···O hydrogen bond resulted in the formation of polar columns in salt **8**. CH···π interactions between the methoxy group and the 1-naphthyl group of the neighbouring MαNP anion assisted in aligning the crystals. In addition, the 1-naphthyl and phenyl groups of salt **8** formed a hydrophobic layer through aromatic CH···π interactions.

The methoxy-assisted salt bridge in the more-soluble diastereomeric salt **9** also bound (*S*)-MαNP and (*R*)-PEA ions without any overlap between the 1-naphthyl and phenyl groups. Instead, the (*S*)-MαNP and (*R*)-PEA ions formed another ion pair *via* a normal salt bridge, a CH···O hydrogen bond, and a π···π interaction. This ion pair formed a motif similar to a sandwich herringbone *via* aromatic CH···π interactions between the 1-naphthyl groups. The salt bridges, NH···O hydrogen bond, and CH···O hydrogen bond created a polar layer in salt **9**.

The NOESY spectra of amides **11** and **12** suggested the higher rotational freedom of the 2-naphthyl group than the 1-naphtyl group. Positive and negative $\Delta\delta$ values were observed on both sides of MβNP plane, demonstrating the applicability of ^{1}H NMR anisotropy to the determination of relative stereochemistry. HPLC profiles showed that the MβNP amides **11** and **12**, which possessed 2-naphthyl groups and were more efficiently separated, were less polar than the MαNP amides.

These findings have elucidated the chiral recognition mechanisms of MαNP salts, and can be used in the crystal engineering of 2-aryl-2-methoxypropanoic acid derivatives for the development of single-enantiomer biofunctional molecules, agrochemicals, and pharmaceuticals.

Experimental

Materials and methods

NMR spectra were obtained with a Bruker Avance 800 spectrometer (Bruker BioSpin, Rheinstetten, Germany) equipped with a cryoprobe. The ^{1}H NMR chemical shifts were reported relative to trimethylsilane (TMS). ^{13}C NMR spectra were obtained with ^{1}H composite pulse decoupling. IR spectra were recorded with a Freexact-II spectrometer (Horiba, Kyoto, Japan) equipped with a diamond ATR accessory, or an FTIR-8200 spectrophotometer (Shimadzu, Kyoto, Japan) with a potassium bromide cell. MS data were obtained with an Apex 70e ESI-FTICR MS instrument (Bruker Daltonics, Bremen, Germany) in positive ion mode. HPLC was performed using an LC10AT VP system (Shimadzu) and a silica SG80 column (250 mm × 4.6 mm I.D.; Shiseido, Tokyo, Japan) with a line filter (column savor; Supelco, Pennsylvania, USA).

Preparation of salt 8

A solution of (*R*)-**1** (31.4 mg, 136 μmol) and (*R*)-**7** (17.3 mg, 143 μmol) in methanol–chloroform (1 : 1, v/v; 6 mL) was partially concentrated in vacuo at 45 °C. The solution was kept at room temperature for 18 h. After the removal of mother liquor from the mixture, salt **8** (8.5 mg, 24 μmol) was obtained as colourless crystals in 18% yield.

(*R*)-1-Phenylethylammonium (*R*)-2-methoxy-2-(1-naphthyl)-propanoate 8. IR (diamond ATR): ν_{max}/cm^{-1} 3200–2300, 1612, 1572, 1531, 1454, 1385, 1375, 1354, 1344, 1140, 1047. $[\alpha]_D^{27}$ −55.2 (*c* 0.235, methanol). Elemental analysis. Found: C, 75.27; H, 7.27; N, 3.92. Calc. for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99%.

Preparation of salt 9

A solution of (*S*)-**1** (64.6 mg, 281 μmol) and (*R*)-**7** (34.2 mg, 282 μmol) in methanol–chloroform (1 : 1, v/v; 4 mL) was partially concentrated in vacuo at 45 °C. After the addition of seed crystals, the solution was kept at room temperature for 18 h. After the removal of mother liquor from the mixture, the crystals were washed with cold ethanol (*ca.* 0.5 mL). This procedure yielded salt **9** (32.4 mg, 92 μmol) as colourless crystals in 33% yield.

(*R*)-1-Phenylethylammonium (*S*)-2-methoxy-2-(1-naphthyl)-propanoate 9. IR (diamond ATR): ν_{max}/cm^{-1} 3200–2300, 1608, 1560, 1535, 1444, 1387, 1369, 1352, 1340, 1330, 1240, 1095, 1041. $[\alpha]_D^{29}$ + 61.7 (*c* 0.373, methanol). Elemental analysis. Found: C, 75.14; H, 7.16; N, 3.92. Calc. for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99%.

X-Ray crystallography

Single crystals of salts **8** and **9** were covered by paraffin oil and mounted on a glass fiber. All data were collected at 123 K on a Rigaku Mercury CCD detector, with monochromatic Mo-Kα radiation, operating at 50 kV/40 mA. Data were processed on a PC using CrystalClear Software (Rigaku, Tokyo, Japan). Structures were solved by direct methods and refined by full-matrix least-squares methods on F^2 (SHELXL-97). CCDC 801461 (salt **8**) and CCDC 801460 (salt **9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

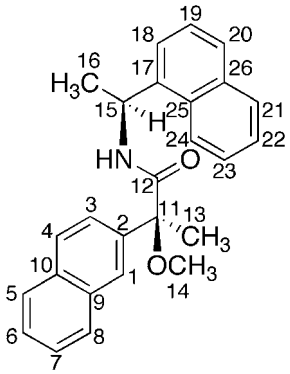
Preparation of amides 11 and 12

Amide **11** (14.7 mg, 38.3 μmol, 45%) and amide **12** (14.9 mg, 38.9 μmol, 46%) were prepared from (*RS*)-**2** (19.6 mg, 85.1 μmol) and (*S*)-**10** (53.6 mg, 313 μmol) with 4-dimethylaminopyridine (DMAP, 82.1 mg, 672 μmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC·HCl, 85.2 mg, 444 μmol), and dichloromethane (0.5 mL). The reaction time was 18 h. See ref. 11 for details.

View Online

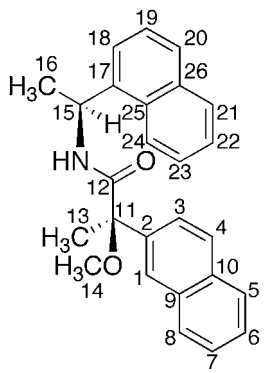
Published on 21 April 2011 on http://pubs.rsc.org | doi:10.1039/C1CE05155E
Downloaded on 18 May 2011

(*S*)-2-Methoxy-2-(2-naphthyl)-*N*-[(*S*)-1-(1-naphthyl)ethyl]propanamide 11.



^{1}H NMR (800 MHz, chloroform-*d*): δ 8.13 (1H, br d, $J = 8$ Hz, 24-H), 7.94 (1H, br s, 1-H), 7.88 (1H, br d, $J = 8$ Hz, 21-H), 7.87 (1H, m, 8-H), 7.86 (1H, m, 4-H), 7.84 (1H, m, 5-H), 7.82 (1H, br d, $J = 8$ Hz, 20-H), 7.57 (1H, dd, $J = 8$, 2 Hz, 3-H), 7.56 (1H, br d, $J = 7$ Hz, 18-H), 7.55 (1H, ddd, $J = 8$, 7, 1 Hz, 23-H), 7.51 (1H, ddd, $J = 8$, 7, 1 Hz, 22-H), 7.49 (1H, m, 6-H), 7.49 (1H, m, 7-H), 7.48 (1H, m, 19-H), 7.25 (1H, m, –NH–), 5.90 (1H, dq, $J = 8.5$, 7 Hz, 15-H), 3.10 (3H, s, 14-H), 1.85 (3H, s, 13-H), 1.61 (3H, d, $J =$ 7 Hz, 16-H). ^{13}C NMR (201 MHz, chloroform-*d*): δ 172.26 (C12), 138.39 (C17), 138.29 (C2), 133.90 (C26), 133.10 (C9), 132.90 (C10), 131.20 (C25), 128.74 (C21), 128.31 (C8*, *assignment interchangeable), 128.30 (C20*), 128.21 (C4), 127.50 (C5), 126.42 (C23), 126.18 (C6), 126.11 (C7), 125.84 (C22), 125.60 (C1), 125.21 (C19), 123.94 (C3), 123.56 (C24), 122.58 (C18), 81.97 (C11), 51.18 (C14), 44.29 (C15), 20.61 (C16), 20.41 (C13). IR (KBr, chloroform): ν_{max}/cm^{-1} 3412, 3061, 3009, 1670, 1506, 1194, 1067. $[\alpha]_D^{28}$ + 54.7 (*c* 0.478, chloroform). MS (ESI–FTICR, positive): *m*/*z* 406.1777 ([M + Na]$^+$, 100%). Calc. for $C_{26}H_{25}NO_2Na$: 406.1778.

(*R*)-2-Methoxy-2-(2-naphthyl)-*N*-[(*S*)-1-(1-naphthyl)ethyl]propanamide 12.



^{1}H NMR (800 MHz, chloroform-*d*): δ 7.83 (1H, br d, $J = 8$ Hz, 21-H), 7.79 (1H, m, 1-H), 7.79 (1H, m, 5-H), 7.78 (1H, br d, $J = 8$ Hz, 20-H), 7.78 (1H, br d, $J = 8$ Hz, 24-H), 7.70 (1H, m, 8-H), 7.68 (1H, br d, $J = 8$ Hz, 4-H), 7.48 (1H, br d, $J = 7$ Hz, 18-H), 7.46 (1H, m, 6-H), 7.46 (1H, m, 7-H), 7.40 (1H, m, 19-H), 7.40 (1H, m, 22-H), 7.36 (1H, dd, $J = 8$, 2 Hz, 3-H), 7.25 (1H, m, –NH–), 7.16 (1H, ddd, $J = 8$, 7, 1 Hz, 23-H), 5.83 (1H, dq, $J =$ 8.3, 7 Hz, 15-H), 3.13 (3H, s, 14-H), 1.94 (3H, s, 13-H), 1.73 (3H, d, $J = 7$ Hz, 16-H). ^{13}C NMR (201 MHz, chloroform-*d*): δ 172.09 (C12), 137.99 (C17), 137.77 (C2), 133.79 (C26), 133.01 (C9), 132.91 (C10), 131.25 (C25), 128.48 (C21), 128.31 (C20), 128.31 (C8), 128.02 (C4), 127.41 (C5), 126.38 (C23), 126.12 (C6), 125.97 (C7), 125.79 (C1), 125.75 (C22), 125.02 (C19), 124.17 (C3), 123.63 (C24), 122.54 (C18), 81.92 (C11), 51.04 (C14), 44.32 (C15), 20.37 (C16), 20.07 (C13). IR (KBr, chloroform): ν_{max}/cm^{-1} 3411, 3059, 3011, 1668, 1506, 1144, 1132. $[\alpha]_D^{29}$ −109 (*c* 0.483 chloroform). MS (ESI–FTICR, positive): *m*/*z* 406.1776 ([M + Na]$^+$, 100%). Calc. for $C_{26}H_{25}NO_2Na$: 406.1778.

Preparation of amide 11

Amide **11** (9.1 mg, 24 μmol) was prepared from (*S*)-**2** (6.3 mg, 27 μmol) and (*S*)-**10** (108.3 mg, 632 μmol) with DMAP (81.7 mg, 669 μmol), EDC·HCl (80.0 mg, 417 μmol), and dichloromethane (0.5 mL) in 87% yield. The reaction time was 18 h. See ref. 11 for details.

Acknowledgements

The authors are grateful to Ms. I. Maeda (NFRI), Dr T. Hatta (JIRCAS) and Ms. S. Nemoto (JIRCAS) for the measurements of NMR and IR spectra, respectively.

Notes and references

1 N. Harada, *Chirality*, 2008, **20**, 691.
2 A. Ichikawa and H. Ono, in *Stereochemistry Research Trends*, ed. M. A. Horvat and J. H. Golob, Nova, New York, 2008, pp. 51–88.
3 S. Sekiguchi, J. Naito, H. Taji, Y. Kasai, A. Sugio, S. Kuwahara, M. Watanabe and N. Harada, *Chirality*, 2008, **20**, 251.
4 A. Ichikawa, S. Hiradate, A. Sugio, S. Kuwahara, M. Watanabe and N. Harada, *Tetrahedron: Asymmetry*, 1999, **10**, 4075.
5 A. Ichikawa and H. Ono, *J. Chromatogr., A*, 2006, **1117**, 38.
6 A. Ichikawa and H. Ono, *Tetrahedron: Asymmetry*, 2005, **16**, 2559.
7 J. M. Seco, E. Quiñoá and R. Riguera, *Chem. Rev.*, 2004, **104**, 17.
8 T. Kusumi, H. Takahashi, P. Xu, T. Fukushima, Y. Asakawa, T. Hashimoto, Y. Kan and Y. Inouye, *Tetrahedron Lett.*, 1994, **35**, 4397.
9 S. Kuwahara, J. Naito, Y. Yamamoto, Y. Kasai, T. Fujita, K. Noro, K. Shimanuki, M. Akagi, M. Watanabe, T. Matsumoto, M. Watanabe, A. Ichikawa and N. Harada, *Eur. J. Org. Chem.*, 2007, 1827.
10 A. Ichikawa, H. Ono and Y. Mikata, *Tetrahedron: Asymmetry*, 2008, **19**, 2693.
11 A. Ichikawa, H. Ono, M. Takenaka and Y. Mikata, *CrystEngComm*, 2010, **12**, 2261.
12 G. R. Desiraju, *Chem. Commun.*, 1997, 1475.
13 G. R. Desiraju and A. Gavezzotti, *J. Chem. Soc., Chem. Commun.*, 1989, 621.
14 D. Das and G. R. Desiraju, *Chem.–Asian J.*, 2006, **1**(1–2), 231.
15 J. Goto, M. Hasegawa, S. Nakamura, K. Shimada and T. Nambara, *J. Chromatogr.*, 1978, **152**, 413.
16 K. Sakai, *Chemistry & Chemical Industry*, 2004, **57**, 507 (in Japanese).
17 A. M. Rouhi, *Chem. Eng. News*, 2003, **81**, 45.
18 K. Saigo, *J. Syn. Org. Chem., Jpn.*, 2006, **64**, 1240 (in Japanese).
19 Y. Kobayashi and K. Saigo, *J. Am. Chem. Soc.*, 2005, **127**, 15054.
20 H. Nohira, K. Saigo, M. Nohira and D. Terunuma, *Optically active compounds—Industrial Organic Chemistry thereof*(in Japanese), Asakura-Shoten, Tokyo, 1989, section 3.
21 K. Sakai, R. Sakurai, A. Yuzawa, Y. Kobayashi and K. Saigo, *Tetrahedron: Asymmetry*, 2003, **14**, 1631.
22 G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2311.
23 T. F. Headen, C. A. Howard, N. T. Skipper, M. A. Wilkinson, D. T. Bowron and A. K. Soper, *J. Am. Chem. Soc.*, 2010, **132**, 5735.

 This journal is © The Royal Society of Chemistry 2011

View Online

24 S. Grimme, *Angew. Chem., Int. Ed.*, 2008, **47**, 3430.
25 S. Tsuzuki, K. Honda, T. Uchimaru, M. Mikami and K. Tanabe, *J. Am. Chem. Soc.*, 2002, **124**, 104.
26 T. Steiner, *Angew. Chem., Int. Ed.*, 2002, **41**, 48.
27 G. R. Desiraju, *Acc. Chem. Res.*, 2002, **35**, 565.
28 M. Nishio, Y. Umezawa, K. Honda, S. Tsuboyama and H. Suezawa, *CrystEngComm*, 2009, **11**, 1757.
29 O. Takahashi, Y. Kohno and M. Nishio, *Chem. Rev.*, 2010, **110**, 6049.
30 A. Ichikawa, H. Ono, S. Hiradate, M. Watanabe and N. Harada, *Tetrahedron: Asymmetry*, 2002, **13**, 1167.
31 A. Ichikawa, S. Hiradate, A. Sugio, S. Kuwahara, M. Watanabe and N. Harada, *Tetrahedron: Asymmetry*, 2000, **11**, 2669.
32 Q. He, H. Gomaa, S. Rohani, J. Zhu and M. Jennings, *Chirality*, 2010, **22**, 707.
33 K. Kobayashi and N. Hayashi, *Solid-phase organic chemistry* (in Japanese), Kagakudojin, Kyoto, 2009, section 2.
34 C. R. Calladine and H. R. Drew, *Understanding DNA: The molecule and how it works*, Academic Press, London, 1992, section 2.
35 T. Steiner and W. Saenger, *J. Am. Chem. Soc.*, 1992, **114**, 10146.
36 K. Seki, Y. Ichimura and Y. Imamura, *Macromolecules*, 1981, **14**, 1831.

Published on 21 April 2011 on http://pubs.rsc.org | doi:10.1039/C1CE05155E
Downloaded on 18 May 2011