Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1603–1613

TETRAHEDRON: *ASYMMETRY*

Study on enantiomerically pure 2-substituted *N,N*-dialkyl-1-naphthamides: resolution, absolute stereochemistry, and application to desymmetrization of cyclic *meso* anhydrides

Wei-Min Dai,* Kelly Ka Yim Yeung, Chun Wo Chow and Ian D. Williams

Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

Received 17 May 2001; accepted 6 June 2001

Abstract—The axially chiral 2-substituted *N,N*-diisopropyl-1-naphthamides **1** and **2** were resolved by HPLC over a chiral stationary phase to provide enantiomerically pure atropisomers. The absolute stereochemistry of (–)-*syn*-**1** was determined by X-ray crystallographic analysis of the corresponding (1*S*)-camphanic acid ester derivative. Desymmetrization of cyclic *meso* anhydrides **5a** and **5b** using (–)-*syn*-**1** gave a single diastereomer in good yield.

1. Introduction

Atropisomerism is a phenomenon which arises from the restricted rotation about a single bond.[1a,b] A classical example is the biaryl atropisomers which have been extensively studied as chiral auxiliaries and ligands in asymmetric synthesis and catalysis.[1c] Recently, non-biaryl atropisomers have received considerable attention for their application as chiral reagents, auxiliaries, and ligands.[2] Axially chiral amides have also been the subject of greatly increasing interest in recent years; these amides cover the anilides,[3] the *N*-arylimides,[4] the benzamides,[5] and the 1-naphthamides[6] and have been investigated in either diastereoselective or enantioselective reactions. In particular, Clayden et al. developed the diastereoselective reactions of 2- and 8-substituted 1-naphthamides[6b,c] and the chemical resolution approach to the enantiomerically pure atropisomers of 2-formyl-1-naphthamides.[6d,e,g] The resolved aldehyde was used in an asymmetric transformation.[6e,f] Moreover, other axially chiral C(1)-substituted naphthalenes were also explored.[7] These include the C(1)-vinyl naphthalenes used in enantioselective alkylation (the chirality memory approach),[7a,b] the C(1)-arylsulfinyl naphthalenes used as chiral ligands in asymmetric allylation[7c] and diastereoselective reactions,[7d,e] and 2-methyl-1-naphthylphosphine oxide.[7f] We report herein on the resolution of 2-substituted 1-naphthamides **1** and **2** (Fig. 1), the determination of their absolute stereochemistries and their application to the desymmetrization of cyclic *meso* anhydrides.

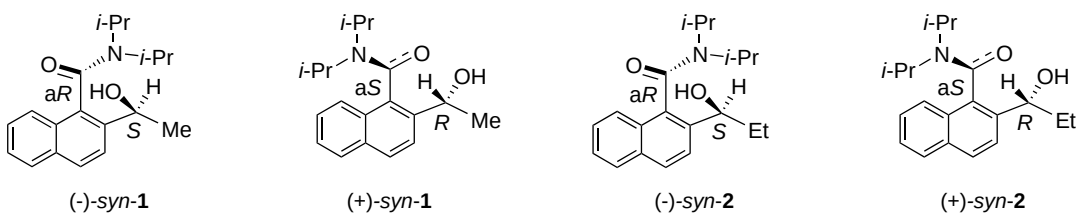

Figure 1. Molecular structures of enantiomerically pure *N,N*-diisopropyl-1-naphthamides **1** and **2**.

* Corresponding author. E-mail: chdai@ust.hk

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PII: S0957-4166(01)00278-6

2. Results and discussion

The racemic amides (±)-**1** and (±)-**2** were prepared as inseparable mixtures of *syn* and *anti* isomers in 93 and 78% yield, respectively, via addition of the Grignard reagents to *N*,*N*-diisopropyl-2-formyl-1-naphthamide (Scheme 1).[8a,9] The *syn*:*anti* ratio was determined to be 91:9 for **1** and 9:1 for **2**, respectively, by HPLC analysis using a chiral stationary phase (Chiralpak AD). Fig. 2 shows the HPLC chromatogram of the racemic *syn*:*anti* mixture of **1**. The retention times for (−)-*syn*-**1** and (+)-*syn*-**1** are 10.2 and 15.5 min, respectively. The *anti* isomers of **1** have retention times of 36.5 and 42.6 min. The diastereoselectivity and chemical yield in our experiment are higher than the reported values of 77:23 (*syn*:*anti*) and 66% for **1**.[8] Chelation-controlled addition of the Grignard reagent to the aldehyde was proposed to account for the *syn* selectivity.[8]

Although the diastereoselective formation of (±)-**1** and (±)-**2** has been reported,[8,10] neither preparation of these alcohols in enantiomerically pure form nor application of these alcohols in asymmetric reactions has been described in the literature. Therefore, we resolved these alcohols by preparative HPLC on a chiral stationary phase (Chiralpak AD) to obtain (−)-*syn*-**1**, (+)-*syn*-**1**, (−)-*syn*-**2**, and (+)-*syn*-**2** in enantiomerically pure form. Moreover, the *syn* stereochemistry of (−)-*syn*-**1** and (+)-*syn*-**2** was confirmed by X-ray crystal structural analyses as shown in Fig. 3. In the crystal structures of (−)-*syn*-**1** and (+)-*syn*-**2**, the amide sub-unit and the naphthalene ring are nearly orthogonal to each other. The alkyl (R = Me or Et) and hydroxyl groups attached to C(1′) are bisected by the naphthalene ring to minimize the steric interaction. Because the C(2)-substituent cannot efficiently block the rotation of the amide moiety around the Ar–C(O)N*i*-Pr_2 single bond, alcohols *syn*-**1** and *syn*-**2** undergo epimerization on heating with energy barriers to rotation of 108.4 and 108.7 kJ mol^{-1} and estimated half-lives of 380 and 410 h in dioxane at 20°C, respectively.[11] Nevertheless, the resolved enantiomerically pure *syn* isomers **1** and **2** can be stored in a refrigerator without causing epimerization.

The absolute stereochemistry of (−)-*syn*-**1** was determined by X-ray crystallographic analysis of the corresponding ester (+)-*anti*-**4** (Scheme 2 and Fig. 4). Condensation of (−)-*syn*-**1** with (−)-(1*S*)-camphanic chloride **3** in the presence of DMAP gave the ester (−)-*syn*-**4**. The latter was found to be an 89:11 mixture of *syn* and *anti* isomers presumably due to slow epimerization of the *syn* isomer during the esterification reaction. It was found that the ester (−)-*syn*-**4** underwent epimerization on heating in EtOAc at 70°C for 1 h to give (+)-*anti*-**4** as a single entity (vide infra). The X-ray crystal structure of (+)-*anti*-**4** is given in Fig. 4, which established the (a*S*) axial chirality for the amide sub-unit and the (*S*) configuration for the C(2) center. Therefore, the absolute stereochemistry of alcohol (−)-*syn*-**1** is determined to be (a*R*,1′*S*). The absolute stereochemistry of (−)-*syn*-**2** was assigned as (a*R*,1′*S*) on the basis of similar HPLC and optical profiles to those of (−)-*syn*-**1**.

Desymmetrization of prochiral or *meso* compounds is an attractive approach to obtain enantiomerically pure molecules for asymmetric synthesis.[12] *meso* Anhydrides are a class of well studied substrates in enzymatic[13] and chemical[14–17] desymmetrization to afford chiral dicarboxylic acid monoesters. Both chiral alcohols[14] and chiral amines [(*S*)-proline esters][15] were employed in the stoichiometric desymmetrization of *meso* anhydrides. The enantioselective transfer of an achiral alkoxide from a Lewis acid–chiral ligand complex to anhydrides was successful and forms a general method to access chiral monoesters of dicarboxylic acids.[16] A recent

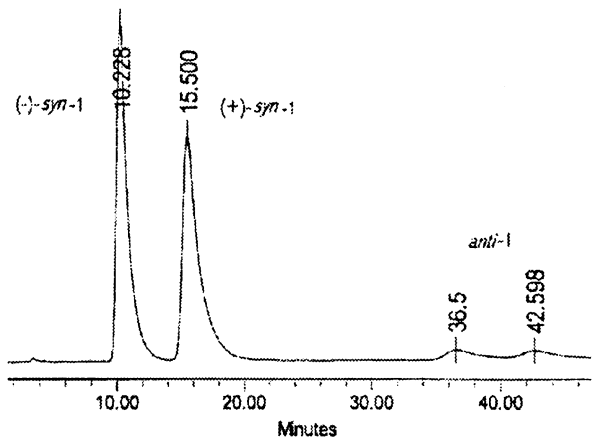
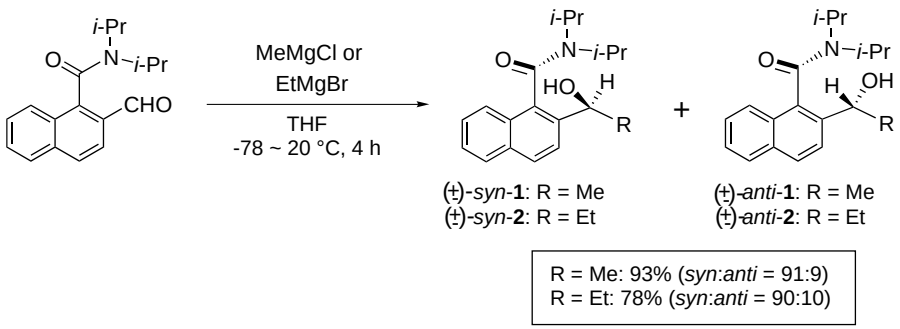


Figure 2. HPLC chromatogram of the racemic mixture of **1** (*syn*:*anti* = 91:9) performed over a Chiralpak AD column eluted with 95:5 hexane/*iso*-propanol at 1 mL min^{-1} and by UV detection at 254 nm.



Scheme 1.

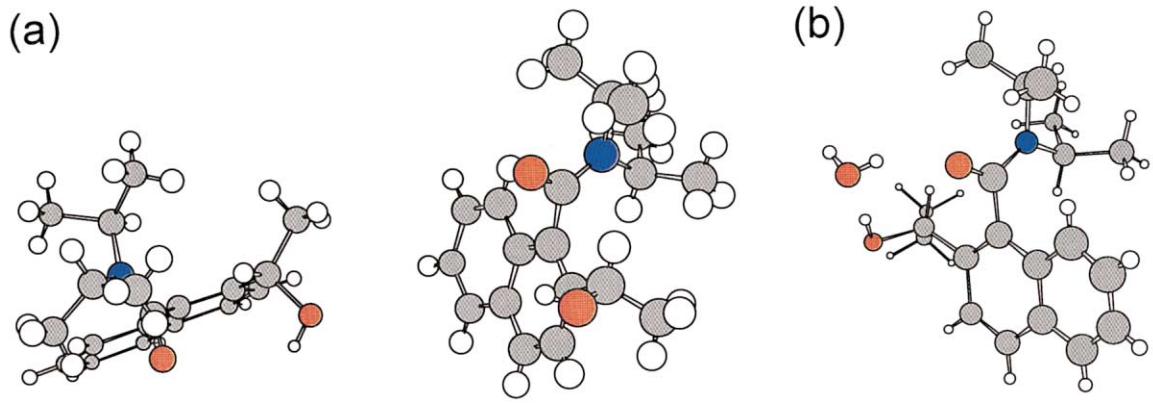
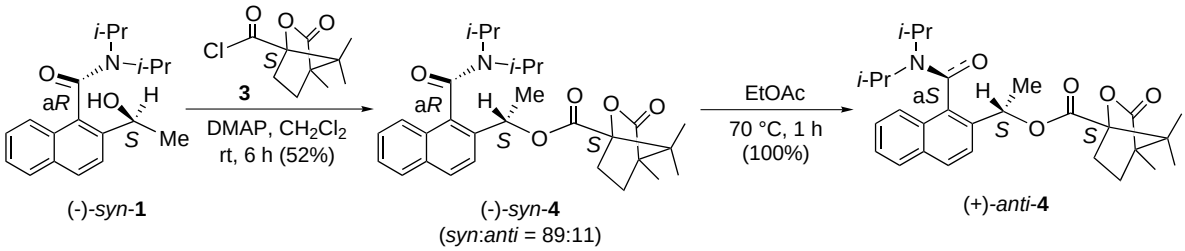


Figure 3. X-Ray crystal structures. (a) Two molecules of (–)-*syn*-**1** in a unit cell and (b) (+)-*syn*-**2** with a bound H_2O.



Scheme 2.

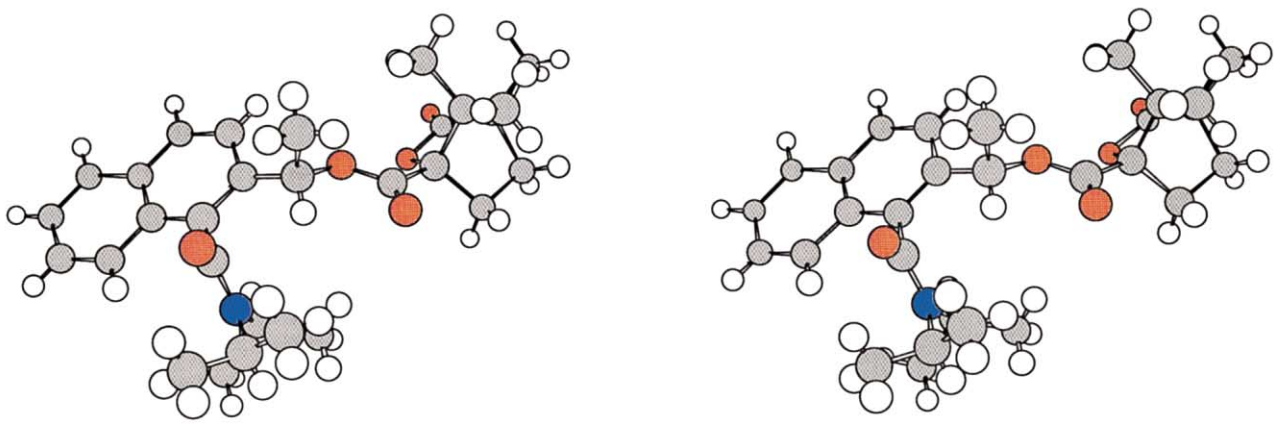
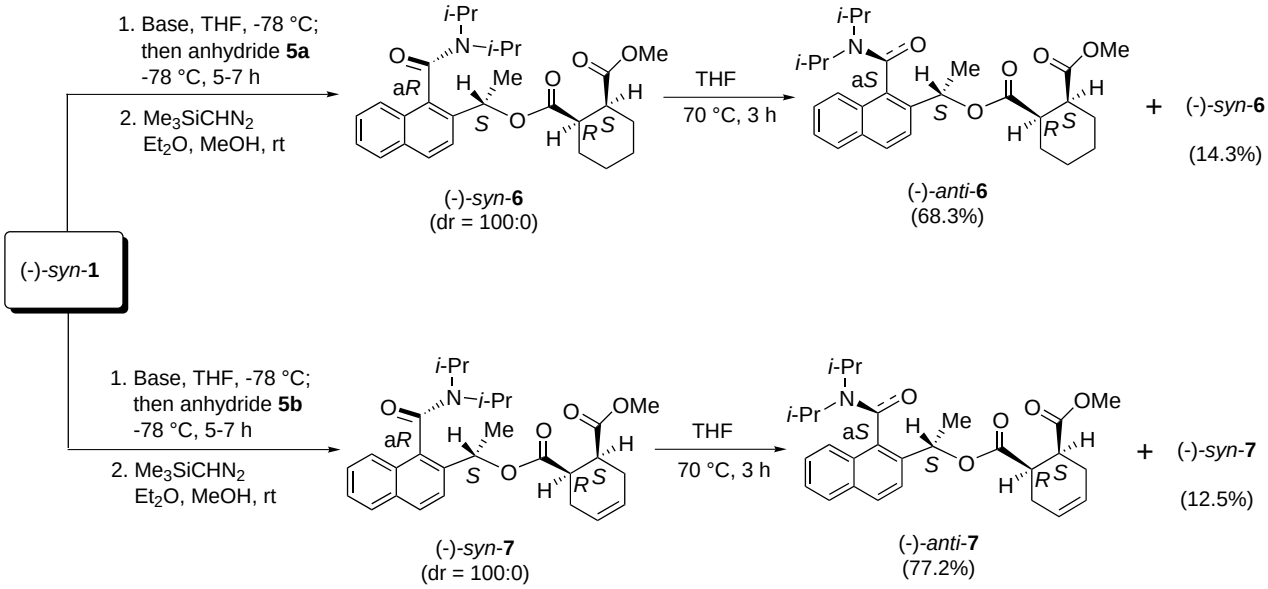


Figure 4. Stereo views of the X-ray crystal structure of the camphanate (+)-*anti*-**4**.

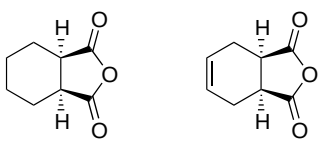
advance in alkaloid-catalyzed desymmetrization of *meso* anhydrides provides a general and efficient route to these chiral monoesters in over 90% e.e.[17g,h]

We envisaged that the molecular architecture of the enantiomerically pure amide (–)-*syn*-**1** would be ideal for the hydroxyl group to engage in highly stereoselective reactions since the dialkyl groups of the amide moiety efficiently differentiate the naphthalene faces (Fig. 3a). We selected *cis*-1,2-cyclohexanedicarboxylic anhydride **5a** and *cis*-1,2,3,6-tetrahydrophthalic anhydride **5b** as the substrates of the asymmetric desymmetrization reactions shown in Scheme 3 and Table 1. Reaction of the lithium alkoxide formed by deprotonation of (–)-*syn*-**1** with *n*-BuLi at –78°C with 1.2 equiv. of **5a** at –78°C for 5 h provided the monoacid. The crude product was then treated with Me_3SiCHN_2 in Et_2O–MeOH[18] to furnish the diester (–)-*syn*-**6** in 41% isolated yield as a single diastereomer. Similarly, (–)-*syn*-**7** was exclusively formed from the lithium salt of (–)-*syn*-**1** and **5b** in 27% isolated yield. In both reactions, we recovered a substantial amount of the chiral alcohol (entries 1 and 4, Table 1). Modifications on the reaction time, temperature, and stoichiometric ratio of the reactants failed to improve the conversion of the chiral alcohol when *n*-BuLi was used as the base. We found that the reaction stopped at ca. 40–50% conversion of (–)-*syn*-**1** under a variety of reaction conditions. These observations led us to suspect that the bulky alkoxide **8**, in addition to attack at the carbonyl group of the anhydrides (path *a*), may remove an α proton from the anhydrides to form the enolates **9a** and **9b**



Scheme 3.

Table 1. Desymmetrization of *meso* anhydrides **5a** and **5b** by (−)-*syn*-**1** under basic conditions



5a **5b**

Entry	Substrate	Base	Product, yield (%)[a]	(−)-*syn*-**1** (%)[b]
1	**5a**	*n*-BuLi	(−)-*syn*-**6**, 41	55
2	**5a**	NaH	(−)-*syn*-**6**, 55	21
3	**5a**	KH	(−)-*syn*-**6**, 71	20
4	**5b**	*n*-BuLi	(−)-*syn*-**7**, 27	48
5	**5b**	KH	(−)-*syn*-**7**, 61	32

[a] Isolated yield of the product.
[b] Recovered starting material after the reaction.

(path *b*) as the competitive side reaction (Fig. 5). If this is the case, the counter metal cation (M^+) should influence the reactivity of the alkoxide **8** toward nucleophilic attack. In order to verify this assumption, we used NaH and KH in place of *n*-BuLi to deprotonate (−)-*syn*-**1** to form the corresponding sodium and potassium alkoxides. We were delighted to find that chemical yields of the product (−)-*syn*-**6** were improved significantly to 55 and 71% in the reactions of the sodium and potassium alkoxide **8** (M = Na, K) with **5a**, respectively (entries 2 and 3, Table 1). Similarly, reaction of the potassium alkoxide **8** (M = K) with **5b** provided (−)-*syn*-**7** in 61% yield (entry 5, Table 1). Under these conditions, the recovered chiral alcohol (−)-*syn*-**1** decreased to 20–32% compared to 48–55% in the reactions of the lithium alkoxide. These results demonstrated that the chemical yield parallels with the nucleophilicity of the alkoxide **8** in the order of K>Na>Li. The absolute stereochemistry of esters (−)-*syn*-**6** and (−)-*syn*-**7** was confirmed as described below and the stereochemical outcome of the desymmetrization is rationalized in Fig. 5. The alkoxide **8** should approach the anhydrides **5a** and **5b** from the convex face in such a manner to minimize the steric interaction. In the case of the sodium and potassium alkoxides, these larger cations may coordinate with the amide carbonyl oxygen to form chelation complexes (not shown for **8** in Fig. 5). Such chelation was proposed to be responsible for the high *syn* selectivity in the formation of alcohols **1** and **2** (Scheme 1).[8] To some extent, chelation between the metal cation and the amide carbonyl oxygen should also increase the nucleophilicity of the alkoxide **8**. We believe that the axial chirality of **8** assists in the desymmetrization of the enantiotopic carbonyl groups because the amide moiety of *syn*-**1** restricts the conformational freedom of the C(2) substituent (see the crystal structure in Fig. 3a). This should result in a better stereochemical differentiation with the anhydrides. There are precedents in the literature which demonstrate that immobilization of the chiral alkoxide conformation via chelation dramatically enhances diastereoselectivity.[14c,e] Ohshima and Mukaiyama[14c] used the diphenylboric ester of (*R*)-2-methoxy-1-phenylethanol in the reactions with **5a** and **5b** in toluene at 0°C to achieve d.r.s of 99.5:0.5 and 19:1, respectively. These authors proposed a rigid five-membered ring chelation structure for the superb performance of the diphenylboric ester of (*R*)-2-methoxy-1-phenylethanol compared with the diphenylboric esters of (*R*)-1-phenylethanol and (*R*)-methyl mandelate. Taguchi et al.[14e] provided another example of highly asymmetric desymmetrization of **5a** and **5b** (both in d.r. of 96:4) using the sodium salt of (*S*)-1-phenyl-3,3-bis(trifluoromethyl)propan-1,3-diol in toluene at −78°C. Again, a six-membered chelate ring structure was suggested to control the selectivity of the reaction.

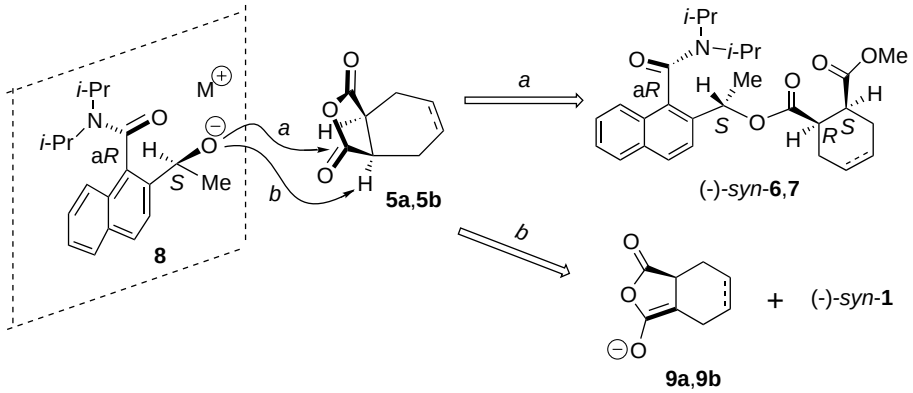


Figure 5. Proposed reaction pathways for the alkoxide **8** formed by deprotonation of (−)-*syn*-**1**. Path *a* is for **8** to attack at the carbonyl group of the anhydride **5a** or **5b**; path *b* is for **8** to remove an α proton from the anhydride **5a** and **5b** to form the enolates **9a** or **9b**, resulting in recovery of (−)-*syn*-**1**.

We found that the esters (−)-*syn*-**6** and (−)-*syn*-**7** underwent epimerization in refluxing THF (70°C for 3 h) to give equilibrium mixtures with the corresponding *anti* isomers (Scheme 3). The isolated yields are 68 and 14% for (−)-*anti*-**6** and (−)-*syn*-**6** and 77 and 13% for (−)-*anti*-**7** and (−)-*syn*-**7**. The absolute stereochemistry of (−)-*anti*-**6** was established by X-ray crystallographic analysis to be (a*S*,1′*S*,1″*R*,2″*S*) (Fig. 6a) where the axial chirality is inversed compared to (a*R*) of the alcohol (−)-*syn*-**1**. We separately synthesized the enantiomer (+)-*anti*-**7** from (+)-*syn*-**1** and the known (1*S*,2*R*)-cyclohex-4-ene-1,2-carboxylic acid monomethyl ester **10**[17f] shown in Scheme 4. The quinine-catalyzed enantioselective methanolysis of the anhydride **5b** afforded **10** in 74% e.e.[19] Condensation of 1.3 equiv. of **10** with (+)-*syn*-**1** under DCC–DMAP conditions gave (+)-*syn*-**7**. Upon heating at 70°C in THF for 3 h, (+)-*syn*-**7** epimerized to (+)-*anti*-**7** whose structure was confirmed by X-ray crystallographic analysis as illustrated in Fig. 6(b). When (−)-*syn*-**1** was condensed with **10** under DCC–DMAP conditions followed by heating, the diastereomer (−)-*anti*-**7**′ was obtained in 50% overall yield (Scheme 4). Therefore, the absolute stereochemistry of (−)-*anti*-**7** was unequivocally assigned as depicted in Scheme 3.

Epimerization of the *syn* esters **4**, **6**, and **7** into their corresponding *anti* isomers is an interesting phenomenon and deserves discussion here. Because we do not have the crystal structures of *syn* esters, two model compounds *syn*-**11** and *anti*-**11** were selected for computational calculations using Chem3D software and their relative stability was compared. The optimized structures are shown in Fig. 7(a). We found that *anti*-**11** resembles the crystal structures of the *anti*-esters **4**, **6**, and **7** and is more stable than the *syn* isomer by 0.66 kcal mol^{-1}. Steric interaction among the methyl group of the C(2) substituent and the alkyl group(s) of the C(1) amide moiety appears to be the main factor which destabilizes the *syn* esters (Fig. 7b). We may assume that the experimentally isolated yields for epimerization of (−)-*syn*-**6** and (−)-*syn*-**7** at 70°C shown in Scheme 3 roughly correlate to their equilibrium ratios. Therefore, the energy difference between (−)-*syn*-**6** and (−)-*anti*-**6** (K=ca. 4.78) or (−)-*syn*-**7** and (−)-*anti*-**7** (K=ca. 6.14) is in the range of 1.07–1.24 kcal mol^{-1} in favor of the *anti* isomers. Equilibrium constants for racemic alcohols *syn*-**1** and *syn*-**2** were measured to be 1.60 (at 62°C) and 1.40 (at 55°C) in dioxane, respectively.[11] The rather small bias for the *anti* alcohols compared to the *anti* esters may reflect the contribution of the intramolecular hydrogen bond to the stability of the *syn* alcohols. Moreover, the carboxylic acid units of the esters **4**, **6**, and **7** slightly modify the relative stability of the *syn* and *anti* atropisomers. With a bulky camphanic moiety in (−)-*syn*-**4**, the *anti* ester (+)-*anti*-**4**

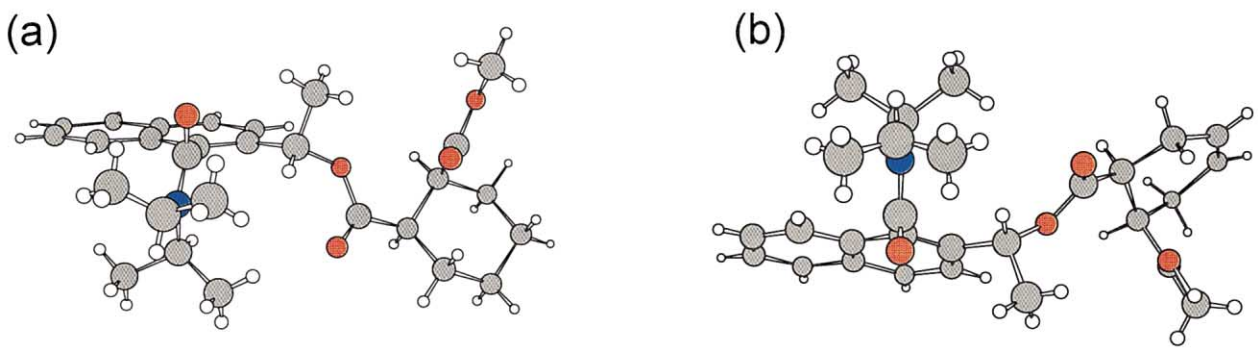


Figure 6. X-Ray crystal structures of (−)-*anti*-**6** (a) and (+)-*anti*-**7** (b).

is much more energetically favored and became the only isolated product for the epimerization of (−)-*syn*-**4** illustrated in Scheme 2. The small amount of (−)-*syn*-**4** could be lost during column chromatographic purification.

3. Conclusion

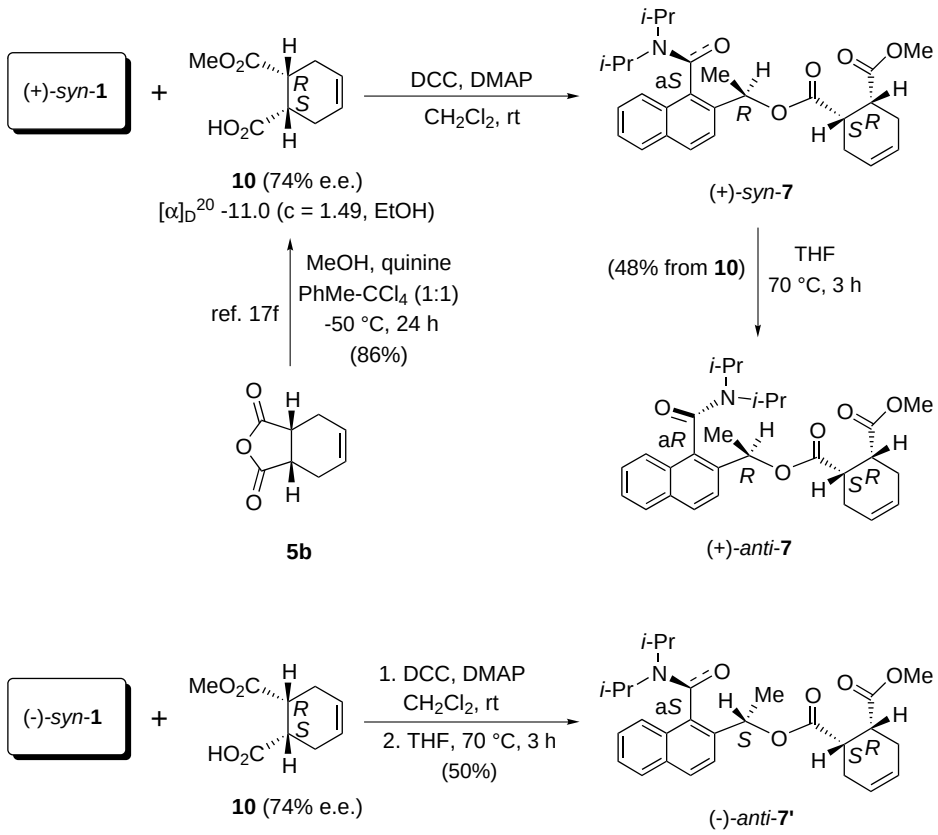
In summary, we have resolved 2-substituted *N*,*N*-dialkyl-1-naphthamides into enantiomerically pure atropisomers and determined their stereochemistry by X-ray crystallographic analysis. These results are a useful reference source for future research into this class of non-biaryl atropisomers. The amides **1** and **2** possess two stereogenic elements, a stereogenic center at the C(2) substituent and a stereogenic axis. The molecular architecture and conformational stability[11] make these axially chiral amides promising source of chirality for asymmetric reactions. We have demonstrated a highly diastereoselective desymmetrization of cyclic *meso* anhydrides **5a** and **5b** using (−)-*syn*-**1** to provide enantiomerically pure esters (−)-*syn*-**6** and (−)-*syn*-**7** in good yields. Moreover, epimerization of the *syn* esters was observed at 70°C to afford the thermodynamically more stable *anti* esters. Studies on practical resolution methods to access enantiomerically pure atropisomeric amides are currently underway in our laboratory.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (300 or 400 MHz for ^{1}H and 75 or 100 MHz for ^{13}C, respectively) with $CHCl_3$ as the internal reference. IR spectra were taken on a FT-IR spectrophotometer. Mass spectra (MS) were measured by the CI method. Elemental analyses were performed by Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences. All reactions were carried out under a nitrogen atmosphere and monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60 F-254) using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Reagents were obtained commercially and used as received. Room temperature is around 20°C.

4.1. General procedure for synthesis and HPLC resolution of racemic alcohols 1 and 2: preparation of (a*R*,1′*S*)-, (a*S*,1′*R*)- and (a*R**,1′*R**)-*N*,*N*-diisopropyl-2-(1′-hydroxyethyl)-1-naphthamide (−)-*syn*-1, (+)-*syn*-1, and (±)-*anti*-1

To a solution of *N*,*N*-diisopropyl-2-formyl-1-naphthamide[8] (594.0 mg, 2.1 mmol) in THF (15 mL)



Scheme 4.

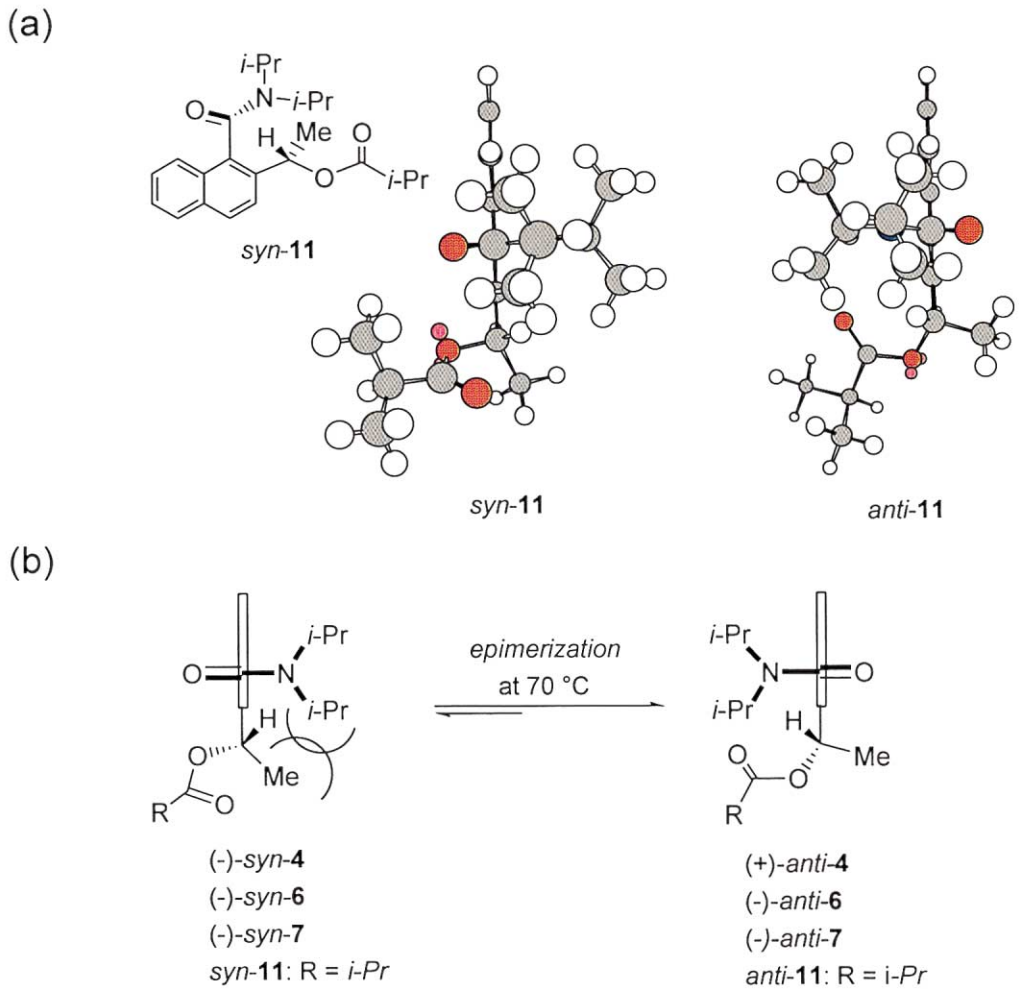


Figure 7. (a) The optimized structures of the model esters *syn*-**11** and *anti*-**11** using Chem3D software. The *anti* isomer is more stable by 0.66 kcal mol^{-1}. (b) Equilibria between *syn* and *anti* esters **4**, **6**, **7**, and **11** via rotation around the Ar–C(O)N*i*-Pr$_2$ single bond on heating.

cooled in a dry ice–acetone bath (ca. −78°C) was added methylmagnesium chloride (3.0 M solution in THF, 1.4 mL, 4.2 mmol) followed by stirring at the same temperature for 2 h. The reaction mixture was allowed to warm up to rt gradually and stirred for another 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution (2×10 mL) and extracted with EtOAc (3×25 mL). The combined organic layer was washed with brine (2× 15 mL), dried over anhydrous $MgSO_4$, filtered, and condensed under reduced pressure. The residue was purified by flash column chromatography (silica gel, 30% EtOAc–hexane) to afford **1** (583.0 mg, 93%) as a 91:9 *syn* and *anti* isomers (see Fig. 2): colorless crystalline solid; R_f=0.44 (60% EtOAc–hexane). In another run, the ratio of *syn* and *anti* isomers was 84:16.

The enantiomerically pure *syn* isomers of **1** were resolved by HPLC separation over a chiral stationary phase (Chiralpak AD). The HPLC chromatogram is found in Fig. 2. The HPLC settings are as follows: flow rate at 5 mL min^{-1}; UV detection at 254 nm; the solvent system being hexane and isopropanol by the gradient method. Initially, a solvent ratio of 2:98 (*i*-PrOH:hexane) was used. After the (−)-*syn*-**1** was completely eluted out, the solvent ratio was changed to 5:95 (*i*-PrOH:hexane). Once all (+)-*syn*-**1** was eluted out, the solvent ratio of 1:1 (*i*-PrOH:hexane) was used to elute all *anti* isomers. (−)-*syn*-**1**: colorless crystalline solid; mp 142–143°C (Et_2O–hexane); $[\alpha]_D^{20}$=−115.3 (*c* 1.01, $CHCl_3$); R_f=0.44 (60% EtOAc–hexane); IR ($CHCl_3$): 3440 (br), 2979, 1600, 1450, 1372, 1324 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85–7.72 (m, 3H), 7.58 (d, *J*= 8.64 Hz, 1H), 7.53–7.42 (m, 2H), 5.04 (q, *J*=6.45 Hz, 1H), 3.73 (br s, 1H, OH), 3.61 (septet, *J*=6.84 Hz, 1H), 3.52 (septet, *J*=6.57 Hz, 1H), 1.74 (d, *J*=6.81 Hz, 3H), 1.67 (d, *J*=6.78 Hz, 3H), 1.59 (d, *J*=6.48 Hz, 3H), 1.04 (d, *J*=6.15 Hz, 3H), 1.02 (d, *J*=6.24 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 138.1, 133.5, 132.7, 129.1, 128.7, 128.1, 126.6, 126.2, 124.8, 123.2, 66.4, 51.2, 46.3, 21.5, 20.8, 20.5, 20.5, 20.4; MS (+CI): *m*/*z* 300 (M^+ +1, 18), 282 (M^+−OH, 100). Anal. calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.42; H, 8.60; N, 4.49%. The structure of (−)-*syn*-**1** was confirmed by the X-ray crystallographic analysis shown in Fig. 3(a).

(+)-*syn*-**1**: colorless crystalline solid; mp 140–142°C (Et_2O–hexane); $[\alpha]_D^{20}$=+116.4 (*c* 1.09, $CHCl_3$); R_f=0.44 (60% EtOAc–hexane). ^{1}H and ^{13}C NMR data of (+)-*syn*-**1** are identical to those of its enantiomer (−)-*syn*-**1**.

(±)-*anti*-**1**: colorless solid; R_f=0.44 (60% EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87–7.73 (m, 3H), 7.63 (d, J=8.58 Hz, 1H), 7.52–7.42 (m, 2H), 5.09 (q, J=6.33 Hz, 1H), 3.60 (septet, J=6.81 Hz, 1H), 3.57 (septet, J=6.75 Hz, 1H), 2.26 (br s, 1H, OH), 1.74 (d, J=6.81 Hz, 3H), 1.66 (d, J=6.81 Hz, 3H), 1.54 (d, J=6.42 Hz, 3H), 1.09 (d, J=6.66 Hz, 3H), 0.98 (d, J=6.63 Hz, 3H).

4.2. (a*R*,1′*S*)-, (a*S*,1′*R*)- and (*R*$^*_a$,1′*R**)-*N*,*N*-Diisopropyl-2-(1′-hydroxypropyl)-1-naphthamide (−)-*syn*-2, (+)-*syn*-2, and (±)-*anti*-2

Prepared from *N*,*N*-diisopropyl-2-formyl-1-naphthamide and EtMgBr in 78% yield as a 9:1 ratio of *syn* and *anti* isomers of **2**: colorless crystalline solid; R_f= 0.45 (50% EtOAc–hexane).

The enantiomerically pure *syn* isomers of **2** were resolved by HPLC separation over a chiral stationary phase (Chiralpak AD) as described above for **1**. (−)-*syn*-**2**: colorless crystalline solid; mp 94–95°C (Et_2O–hexane); $[\alpha]_D^{20}$=−99.6 (*c* 0.98, $CHCl_3$); R_f=0.45 (50% EtOAc–hexane); IR (CH_2Cl_2): 3413 (br), 2966, 1606, 1448, 1371, 1324, 1209, 1047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88–7.74 (m, 3H), 7.59 (d, J=8.61 Hz, 1H), 7.54–7.43 (m, 2H), 4.73 (t, J=6.81 Hz, 1H), 3.64 (septet, J=6.81 Hz, 1H), 3.58 (septet, J=6.63 Hz, 1H), 3.42 (br s, 1H, OH), 2.18–2.01 (m, 1H), 1.94–1.79 (m, 1H), 1.76 (d, J=6.84 Hz, 3H), 1.70 (d, J=6.81 Hz, 3H), 1.08 (t, J=7.44 Hz, 3H), 1.06 (d, J=6.69 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 137.5, 134.2, 132.7, 129.1, 128.6, 128.1, 126.5, 126.2, 124.8, 123.5, 72.4, 51.3, 46.3, 28.1, 20.7, 20.5 (×2), 20.4, 11.1; MS (+CI): *m*/*z* 314 (M^++1, 55), 296 (100). Anal. calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.25; H, 8.39; N, 4.17%.

(+)-*syn*-**2**: colorless crystalline solid; mp 94–96°C (Et_2O–hexane); $[\alpha]_D^{20}$=+100.9 (*c* 0.98, $CHCl_3$); R_f=0.45 (50% EtOAc–hexane). ^{1}H and ^{13}C NMR data of (+)-*syn*-**2** are identical to those of its enantiomer (−)-*syn*-**2**. The structure of (+)-*syn*-**2** was confirmed by the X-ray crystallographic analysis shown in Fig. 3(b).

(±)-*anti*-**2**: colorless solid; R_f=0.45 (50% EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87–7.73 (m, 3H), 7.60 (d, J=8.64 Hz, 1H), 7.53–7.42 (m, 2H), 4.79 (dd, J=7.14, 5.85 Hz, 1H), 3.58 (septet, J=6.75 Hz, 2H), 2.15 (br s, 1H, OH), 2.00–1.75 (m, 2H), 1.75 (d, J=6.81 Hz, 3H), 1.66 (d, J=6.81 Hz, 3H), 1.11 (d, J=6.66 Hz, 3H), 0.98 (d, J=6.60 Hz, 3H), 0.96 (t, J=7.44 Hz, 3H).

4.3. (−)-(a*R*,1′*S*,1″*S*,4″*R*)-*N*,*N*-Diisopropyl-2-[1′-(4″,7″,7″-trimethyl-3″-oxo-2″-oxabicyclo[2.2.1]heptanecarbonyloxy)ethyl]-1-naphthamide (−)-*syn*-4 and (+)-(a*S*,1′*S*,1″*S*,4″*R*)-*N*,*N*-diisopropyl-2-[1′-(4″,7″,7″-trimethyl-3″-oxo-2″-oxabicyclo[2.2.1]heptanecarbonyloxy)ethyl]-1-naphthamide (+)-*anti*-4

To a solution of the alcohol (−)-*syn*-**1** (42.0 mg, 0.14 mmol) and DMAP (21.0 mg, 0.17 mmol) in dry CH_2Cl_2 (3 mL) cooled in an ice-water bath (ca. 0°C) was added (−)-(1*S*)-camphanic chloride **3** (37.0 mg, 0.17 mmol). The resultant mixture was stirred at rt for 6 h. The reaction mixture was quenched by saturated aqueous NH_4Cl solution (5 mL), extracted with CH_2Cl_2 (3×5 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtrated, and condensed under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc–hexane) to give (−)-*syn*-**4** (31.0 mg, 46%) and (+)-*anti*-**4** (4.0 mg, 6%). The *syn* isomer (−)-*syn*-**4** was completely epimerized into (+)-*anti*-**4** in EtOAc at 70°C for 1 h. (−)-*syn*-**4**: $[\alpha]_D^{20}$=−9.9 (*c* 1.05, $CHCl_3$); R_f=0.30 (20% EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J=8.88 Hz, 1H), 7.86–7.79 (m, 2H), 7.66 (d, J=8.67 Hz, 1H), 7.54–7.48 (m, 2H), 6.27 (q, J=6.48 Hz, 1H), 3.66–2.50 (m, 2H), 2.42–2.33 (m, 1H), 2.05–1.95 (m, 1H), 1.87–1.77 (m, 1H), 1.75 (d, J=6.84 Hz, 3H), 1.71 (d, J=6.48 Hz, 3H), 1.70 (d, J=6.78 Hz, 3H), 1.66–1.56 (m, 1H), 1.14 (d, J=6.69 Hz, 3H), 1.05 (s, 3H), 1.03 (d, J=6.75 Hz, 3H), 1.00 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.5, 167.9, 166.1, 135.1, 133.3, 131.8, 129.3, 128.7, 128.1, 127.0, 126.9, 125.7, 123.7, 91.1, 70.2, 54.8, 54.4, 51.0, 46.4, 30.4, 29.0, 21.1, 20.9, 20.7, 20.6, 20.6, 16.4, 16.2, 9.6.

(+)-*anti*-**4**: colorless crystalline solid; mp 214–215°C (EtOAc–hexane); $[\alpha]_D^{20}$=+49.4 (*c* 0.85, $CHCl_3$); R_f= 0.33 (20% EtOAc–hexane); IR (CH_2Cl_2): 2973, 1790, 1749, 1627, 1445, 1313, 1266, 1168, 1105, 1060 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J=8.80 Hz, 1H), 7.85–7.70 (m, 2H), 7.65 (d, J=8.40 Hz, 1H), 7.53–7.48 (m, 2H), 6.21 (q, J=6.40 Hz, 1H), 3.65–2.51 (m, 2H), 2.46 (ddd, J=14.4, 10.8, 4.40 Hz, 1H), 2.04–1.89 (m, 2H), 1.76 (d, J=7.20 Hz, 3H), 1.75–1.62 (m, 1H), 1.72 (d, J=6.80 Hz, 3H), 1.64 (d, J=6.80 Hz, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 1.04 (d, J=6.80 Hz, 3H), 1.01 (s, 3H), 1.00 (d, J=6.80 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 168.1, 166.5, 133.6, 132.9, 132.8, 129.0, 128.8, 128.1, 126.8, 126.5, 125.1, 123.0, 91.0, 72.4, 54.9, 54.3, 51.3, 46.3, 30.7, 29.0, 23.4, 21.1, 20.9, 20.7, 20.6, 17.0, 16.9, 9.8; MS (+CI): *m*/*z* 480 (M^++1, 57), 282 (100). Anal. calcd for $C_{29}H_{37}NO_5$: C, 72.62; H, 7.78; N, 2.92. Found: C, 72.93; H, 8.24; N, 2.79%. The structure of (+)-*anti*-**4** was confirmed by the X-ray crystallographic analysis shown in Fig. 4.

4.4. General procedure for the enantioselective desymmetrization of cyclic *meso* anhydrides 5a and 5b: synthesis of (−)-(a*R*,1′*S*,1″*R*,2″*S*)-*N*,*N*-diisopropyl-2-[1′-(2″-methoxycarbonylcyclohexane-1″-carbonyloxy)-ethyl]-1-naphthamide (−)-*syn*-6

To a solution of the alcohol (−)-*syn*-**1** (97.0 mg, 0.32 mmol) in dry THF (2 mL) maintained in an ice-water bath (ca. 0°C) was added 35% KH in mineral oil (60 μL, 0.49 mmol) followed by stirring at the same temperature for 1 h. The resultant alkoxide solution was cooled to −78°C in a dry ice–acetone bath. Anhydride **5a** (60.0 mg, 0.39 mmol) was added to the alkoxide followed by stirring at −78°C for 7 h. The reaction was

then quenched by 5% aqueous HCl (3 mL) and extracted with EtOAc (3×5 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained crude monoester was dissolved in a mixed solvent of MeOH–Et_2O (2 mL, 1:1) and the solution was cooled in an ice-water bath (ca. 0°C) followed by addition of a solution of (trimethylsilyl)diazomethane (2.0 M in hexanes, 5 mL). After stirring at rt until bubbling of nitrogen gas from the solution stopped, the reaction mixture was concentrated under reduced pressure to give a yellow solid which was purified by flash column chromatography (silica gel, 20% EtOAc–hexane) to afford (−)-*syn*-**6** (108.0 mg, 71%) along with recovery of the starting material (−)-*syn*-**1** (19.0 mg, 20%) (entry 3, Table 1). The results of the reactions of (−)-*syn*-**6** using *n*-BuLi and NaH as the base for deprotonation are found in Table 1. (−)-*syn*-**6**: colorless crystalline solid; mp 196–197°C (EtOAc–hexane); $[\alpha]_D^{20}=-47.4$ (*c* 0.98, $CHCl_3$); $R_f=0.41$ (20% EtOAc–hexane); IR (CH_2Cl_2): 2936, 1732, 1631, 1443, 1311, 1210, 1169, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.87–7.79 (m, 3H), 7.61 (d, $J=8.40$ Hz, 1H), 7.51–7.47 (m, 2H), 6.14 (q, $J=6.40$ Hz, 1H), 3.67–3.50 (m, 2H), 3.53 (s, 3H), 2.90–2.75 (m, 2H), 2.03–1.90 (m, 1H), 1.82–1.68 (m, 1H), 1.75 (d, $J=6.80$ Hz, 3H), 1.69 (d, $J=6.80$ Hz, 3H), 1.61 (d, $J=6.00$ Hz, 3H), 1.65–1.53 (m, 4H), 1.48–1.30 (m, 2H), 1.13 (d, $J=6.80$ Hz, 3H), 1.01 (d, $J=6.80$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 171.9, 167.8, 134.6, 133.0, 132.5, 129.2, 128.2, 127.8, 126.6, 126.5, 125.4, 124.0, 68.8, 51.3; 50.9; 46.3, 42.7, 42.3, 26.3 (×2), 23.9, 23.4, 21.1, 20.9, 20.6 (×2), 20.4; MS (+CI): *m*/*z* 468 (M^++1, 1), 282 (60), 154 (100). Anal. calcd for $C_{28}H_{37}NO_5$: C, 71.92; H, 7.98; N, 3.00. Found: C, 72.32; H, 8.56; N, 2.94%.

4.5. (−)-(a*R*,1′*S*,1″*R*,2″*S*)-*N*,*N*-Diisopropyl-2-[1′-(2″-methoxycarbonylcyclohex-4″-ene-1″-carbonyloxy)ethyl]-1-naphthamide (−)-*syn*-7

Prepared from the alcohol (−)-*syn*-**1** and anhydride **5b** using KH as the base as described above for synthesis of (−)-*syn*-**6**. (−)-*syn*-**7** was obtained in 61% isolated yield along with recovery of the starting material (−)-*syn*-**1** in 32% yield (entry 5, Table 1). (−)-*syn*-**7**: colorless crystalline solid; mp 183–185°C (EtOAc–hexane); $[\alpha]_D^{20}=-51.0$ (*c* 1.00, $CHCl_3$); $R_f=0.32$ (20% EtOAc–hexane); IR (CH_2Cl_2): 2976, 1733, 1630, 1442, 1312, 1199, 1160, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, $J=8.40$ Hz, 1H), 7.84–7.78 (m, 2H), 7.62 (d, $J=8.80$ Hz, 1H), 7.51–7.47 (m, 2H), 6.15 (q, $J=6.40$ Hz, 1H), 5.70–5.62 (m, 2H), 3.64–3.48 (m, 2H), 3.53 (s, 3H), 3.08–2.97 (m, 2H), 2.58–2.44 (m, 2H), 2.35–2.23 (m, 2H), 1.74 (d, $J=6.80$ Hz, 3H), 1.67 (d, $J=6.80$ Hz, 3H), 1.62 (d, $J=6.40$ Hz, 3H), 1.12 (d, $J=6.80$ Hz, 3H), 1.00 (d, $J=6.40$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 171.4, 167.9, 134.6, 133.1, 132.5, 129.2, 128.3, 127.9, 126.7, 126.5, 125.5, 125.3, 124.6, 124.1, 69.2, 51.6, 51.0, 46.4, 40.0, 39.8, 25.9, 25.6, 21.1, 21.0, 20.6 (×2), 20.5; MS (+CI): *m*/*z* 466 (M^++1, 30), 282 (100). Anal. calcd for $C_{28}H_{35}NO_5$: C, 72.23; H, 7.58; N, 3.01. Found: C, 71.86; H, 7.67; N, 2.65%.

4.6. (−)-(a*S*,1′*S*,1″*R*,2″*S*)-*N*,*N*-Diisopropyl-2-[1′-(2″-methoxycarbonylcyclohexane-1″-carbonyloxy)ethyl]-1-naphthamide (−)-*anti*-6

A solution of (−)-*syn*-**6** (73.2 mg, 0.16 mmol) in THF (5 mL) was heated at 70°C for 3 h. The resultant mixture was concentrated under reduced pressure to give a white solid which was purified by flash column chromatography (silica gel, 10% EtOAc–hexane) to afford (−)-*anti*-**6** (50.0 mg, 68.3%) and the starting material (−)-*syn*-**6** (10.5 mg, 14.3%). (−)-*anti*-**6**: colorless crystalline solid; mp 195–196°C (EtOAc–hexane); $[\alpha]_D^{20}=-0.93$ (*c* 0.54, $CHCl_3$); $R_f=0.54$ (20% EtOAc–hexane); IR (CH_2Cl_2): 2928, 1733, 1627, 1446, 1313, 1262, 1210, 1174, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, $J=8.40$ Hz, 1H), 7.85–7.77 (m, 2H), 7.58 (d, $J=8.40$ Hz, 1H), 7.52–7.46 (m, 2H), 6.07 (q, $J=6.80$ Hz, 1H), 3.67–3.50 (m, 2H), 3.60 (s, 3H), 2.95–2.82 (m, 2H), 2.15–1.93 (m, 2H), 1.88–1.75 (m, 2H), 1.75 (d, $J=6.80$ Hz, 3H), 1.71 (d, $J=6.80$ Hz, 3H), 1.55 (d, $J=6.40$ Hz, 3H), 1.56–1.35 (m, 4H), 1.04 (d, $J=6.80$ Hz, 3H), 0.99 (d, $J=6.40$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 172.2, 168.2, 134.7, 132.7, 132.7, 129.1, 128.4, 128.0, 126.6, 126.2, 125.1, 123.2, 70.8, 51.6; 51.3; 46.3, 42.8, 42.7, 26.6, 26.3, 23.9, 23.7, 23.1, 21.2, 20.7, 20.7, 20.6; MS (+CI): *m*/*z* 468 (M^++1, 15), 282 (100). Anal. calcd for $C_{28}H_{37}NO_5$: C, 71.92; H, 7.98; N, 3.00. Found: C, 71.75; H, 7.81; N, 2.92%. The structure of (−)-*anti*-**6** was confirmed by the X-ray crystallographic analysis shown in Fig. 6(a).

4.7. (−)-(a*S*,1′*S*,1″*R*,2″*S*)-*N*,*N*-Diisopropyl-2-[1′-(2″-methoxycarbonylcyclohex-4″-ene-1″-carbonyloxy)ethyl]-1-naphthamide (−)-*anti*-7

A solution of (−)-*syn*-**7** (50.4 mg, 0.11 mmol) in THF (5 mL) was heated at 70°C for 3 h. The resultant mixture was concentrated under reduced pressure to give a white solid which was purified by flash column chromatography (silica gel, 10% EtOAc–hexane) to afford (−)-*anti*-**7** (38.9 mg, 77.2%) and the starting material (−)-*syn*-**7** (6.3 mg, 12.5%). (−)-*anti*-**7**: colorless crystalline solid; mp 184–185°C (Et_2O–hexane); $[\alpha]_D^{20}=-5.09$ (*c* 1.10, $CHCl_3$); $R_f=0.46$ (20% EtOAc–hexane); IR (CH_2Cl_2): 2931, 1733, 1627, 1442, 1370, 1313, 1207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, $J=8.00$ Hz, 1H), 7.84–7.78 (m, 2H), 7.56 (d, $J=8.80$ Hz, 1H), 7.51–7.47 (m, 2H), 6.07 (q, $J=6.40$ Hz, 1H), 5.68 (s, 2H), 3.64 (s, 3H), 3.64–3.50 (m, 2H), 3.15–3.11 (m, 1H), 3.08–3.03 (m, 1H), 2.66–2.52 (m, 2H), 2.47–2.32 (m, 2H), 1.74 (d, $J=6.80$ Hz, 3H), 1.70 (d, $J=6.80$ Hz, 3H), 1.56 (d, $J=6.80$ Hz, 3H), 1.02 (d, $J=6.40$ Hz, 3H), 0.98 (d, $J=6.80$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 171.7, 168.1, 134.5, 132.8, 132.7, 129.1, 128.4, 127.9, 126.7, 126.3, 125.1, 125.1, 125.1, 123.2, 71.2, 51.8, 51.3, 46.3, 40.0, 39.9, 26.3, 25.7, 22.9, 21.2, 20.7 (×2), 20.6; MS (+CI): *m*/*z* 466 (M^++1, 18), 282 (100). Anal. calcd for $C_{28}H_{35}NO_5$: C, 72.23; H, 7.58; N, 3.01. Found: C, 71.84; H, 7.65; N, 2.66%.

4.8. Synthesis of (1*S*,2*R*)-cyclohex-4-ene-1,2-dicarboxylic acid monomethyl ester 10

To a suspension of anhydride **5b** (0.500 g, 3.37 mmol) and quinine (1.180 g, 3.64 mmol) in a mixed solvent of toluene and CCl_4 (15 mL, 1:1) maintained at −50°C by a chiller under N_2 was added dry MeOH (0.40 mL, 9.88 mmol) dropwise. The resultant mixture was stirred at the same temperature for 24 h. The reaction mixture was condensed, the residue dissolved in EtOAc, and the organic layer washed with 5% HCl (2×10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give **10** (0.538 g, 86%) which was used without further purification. **10**: yellow oil; $[\alpha]_D^{20}=-12.2$ (*c* 1.45, EtOH) which is estimated to possess 74% e.e. according to the reported optical rotation data.[17f]

4.9. (+)-(a*R*,1′*R*,1″*S*,2″*R*)-*N*,*N*-Diisopropyl-2-[1′-(2″-methoxycarbonylcyclohex-4″-ene-1″-carbonyloxy)ethyl]-1-naphthamide (+)-*anti*-7

To a solution of (+)-*syn*-**1** (95.4 mg, 0.32 mmol), **10** (76.0 mg, 0.41 mmol) and DMAP (7.0 mg, 0.06 mmol) in dry CH_2Cl_2 (5 mL) cooled in an ice-water bath (ca. 0°C) was added DCC (79.0 mg, 0.38 mmol). The resultant mixture was allowed to stir at rt for 2 days. The reaction mixture was filtered through Celite with rinsing by a minimum amount of CH_2Cl_2, the combined filtrate concentrated under reduced pressure to give a crude yellow oil. Purification of the crude product by flash column chromatography (silica gel, 15% EtOAc–hexane) afforded the (+)-*syn*-**7** (130.8 mg, 88%). ^{1}H NMR data showed that this sample contains a small amount of inseparable impurity. Therefore, (+)-*syn*-**7** was subjected to epimerization on heating at 70°C as described above for its enantiomer (−)-*syn*-**7**. (+)-*anti*-**7** was obtained in 48% yield on the basis of the amount of (+)-*syn*-**1** used. (+)-*anti*-**7**: colorless crystalline solid; mp 185–186°C (EtOAc–hexane); $[\alpha]_D^{20}=+4.67$ (*c* 0.45, $CHCl_3$). ^{1}H and ^{13}C NMR data of (+)-*anti*-**7** are identical to those of its enantiomer (−)-*anti*-**7**. The structure of (+)-*anti*-**7** was confirmed by the X-ray crystallographic analysis shown in Fig. 6(b).

4.10. (−)-(a*S*,1′*S*,1″*S*,2″*R*)-*N*,*N*-Diisopropyl-2-[1′-(2″-methoxycarbonylcyclohex-4″-ene-1″-carbonyloxy)ethyl]-1-naphthamide (−)-*anti*-7′

Prepared from (−)-*syn*-**1** and **10** (74% e.e.) in 50% overall yield as described above for synthesis of (+)-*anti*-**7**. (−)-*anti*-**7′**: colorless crystalline solid; mp 147–148°C (Et_2O–hexane); $[\alpha]_D^{20}=-12.4$ (*c* 0.48, $CHCl_3$); IR (CH_2Cl_2): 2974, 1732, 1626, 1442, 1370, 1314, 1207 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, $J=8.40$ Hz, 1H), 7.84–7.78 (m, 2H), 7.58 (d, $J=8.40$ Hz, 1H), 7.52–7.45 (m, 2H), 6.10 (q, $J=6.40$ Hz, 1H), 5.72–5.62 (m, 2H), 3.63 (s, 3H), 3.62–3.50 (m, 2H), 3.16–3.03 (m, 2H), 2.70–2.52 (m, 2H), 2.47–2.32 (m, 2H), 1.75 (d, $J=6.80$ Hz, 3H), 1.71 (d, $J=6.80$ Hz, 3H), 1.55 (d, $J=6.40$ Hz, 3H), 1.03 (d, $J=6.80$ Hz, 3H), 0.98 (d, $J=6.80$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 171.9, 168.1, 134.5, 132.8, 132.7, 129.1, 128.4, 128.0, 126.6, 126.2, 125.1, 125.1, 125.0, 123.2, 71.0, 51.7, 51.3, 46.3, 40.1, 39.6, 26.2, 25.8, 23.2, 21.2, 20.7, 20.7, 20.6; MS (+CI): *m*/*z* 466 (M^++1, 17), 282 (100).

Acknowledgements

This work was supported by the Department of Chemistry, HKUST and a Direct Allocation Grant (DAG99/00.SC14) from the Research Grants Council of Hong Kong SAR, China. The authors would also like to thank Dr. Mavis Yuk Ha Lee for assistance on an experiment.

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