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Tetrahedron: *Asymmetry* 14 (2003) 749–756

TETRAHEDRON: *ASYMMETRY*

# Synthesis of a 1,3-spiro-amino-alcohol-derived chiral auxiliary and its application to Diels–Alder reactions

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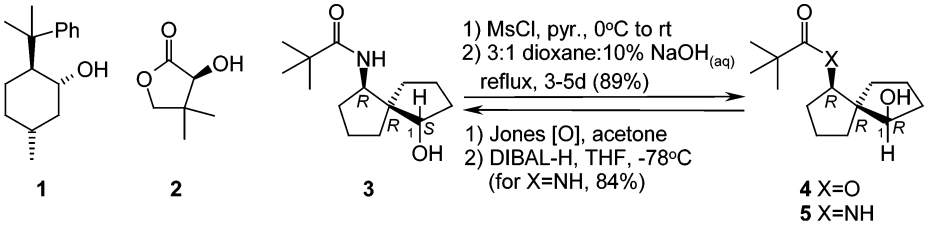
Received 9 December 2002; accepted 1 January 2003

**Abstract**—A short synthesis and resolution of (1*R*,5*R*,6*R*)-6-aminospiro[4.4]nonan-1-ol, **11**, is reported. The pivalamide derivative (+)-**5** gives excellent diastereo- and regiocontrol as well as *endo* selectivity as a chiral auxiliary in the $BCl_3$-catalyzed Diels–Alder reaction with a variety of symmetrical and unsymmetrical dienes. The adducts are readily cleaved by saponification, allowing recovery and reuse of (+)-**5**. 

## 1. Introduction

Much of the recent work involving chiral auxiliaries has focused on oxazolines[1] and related systems. This type of auxiliary offers good to excellent stereocontrol but can be difficult to remove since it is attached via an amide linkage. An ester, on the other hand, can be readily saponified, and as such, alcohols should be prime candidates as chiral auxiliaries. In the Diels–Alder reaction, however, only a few alcohols have shown a reasonable degree of reactivity and stereocontrol over a wide range of symmetrical and unsymmetrical dienes. Of all the chiral auxiliaries reported for use in the Diels–Alder reaction with an acrylate as the dienophile,[2] phenylmenthol **1**[3] and pantolactone **2**[4] have provided the best selection and reactivity to date (Scheme 1). In addition, 1,1- and 1,2-amino alcohols have been used extensively as chiral auxiliaries in a variety of asymmetric transformations;[2b,5] however, very little has been reported with 1,3-amino alcohols.[6] In 2000, we reported that *cis*,*trans*-spiro-amido-alcohol **3**,[7] a 1,3-amino alcohol derivative, gave good selectivity in the Diels–Alder reaction; however, it did not have the optimal geometry for bringing the blocking group into close proximity to the dienophile as was the case with the corresponding *cis*,*cis*-spiro-diol **4**.[8] The epimer of **3** (i.e. **5**) has the ideal *cis*,*cis* geometry. While **3** is an effective auxiliary in its own right,[7a] its synthesis is 10 steps long and is not particularly amenable to scale up. We now report a practical synthesis of **5** as well as its application to the Diels–Alder reaction with a variety of symmetrical and unsymmetrical dienes. We also report that **3** and **5** are complementary auxiliaries that only differ at the stereocenter containing the hydroxyl group. The same sense of chirality at the spiro and amido centers, but differing in the stereochemistry at C-1, led to products that are enantiomeric. This is particularly useful since the hydroxyl group in **3** and **5** is readily epimerized (Scheme 1).




**Scheme 1.**

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0957-4166/03/$ - see front matter 
doi:10.1016/S0957-4166(03)00051-X

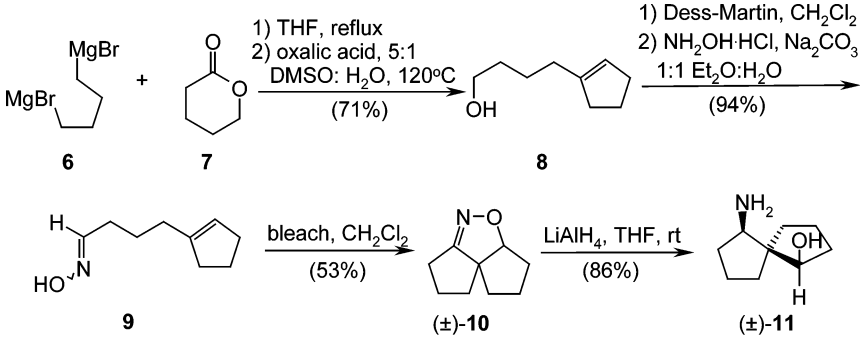
## 2. Results and discussion

Racemic amino alcohol **11** can be prepared with perfect diastereocontrol (Scheme 2) and without the need for purification by chromatography since the amino alcohol can be separated from cyclization by-products via acid–base extraction. δ-Valerolactone **7** is added to Grignard reagent **6** to give a diol,[9] which is dehydrated under acidic conditions to **8**[10] (12:1 mixture of endocyclic:exocyclic double bond isomers). Oxidation to the aldehyde is followed by conversion to oxime **9**. Stirring with bleach subsequently converts the oxime to a nitrile oxide that undergoes intramolecular 1,3-dipolar cycloaddition with the olefin, giving 2-isoxazoline (±)-**10**. At this stage, the undesirable double bond isomer of **8** is unreactive; thus, there is no need to remove it earlier in the synthesis. For the purposes of quantification and characterization, chromatography of (±)-**10** is reported but $LiAlH_4$ reduction of (±)-**10** to (±)-**11** is equally effective on crude (±)-**10**. Since $LiAlH_4$ reduces the C=N bond before cleaving the N–O bond, the *cis*,*cis* geometry of (±)-**5** is enforced by the intermediate with three *cis*-fused pentacycles (not shown).

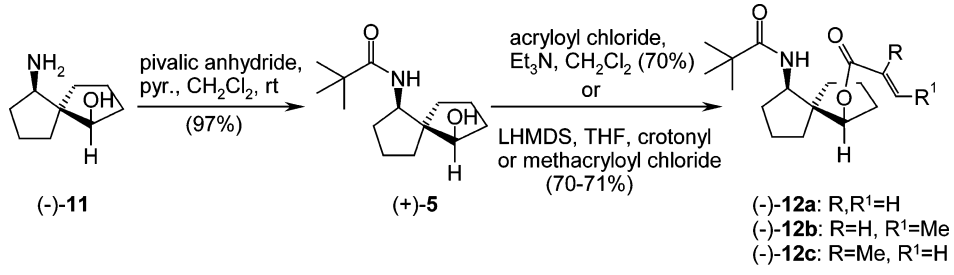
Resolution of (±)-**11** was achieved by co-crystallization with 0.5 equiv. of enantiopure mandelic acid in MeCN. Co-crystallization with (*S*)-(+)-mandelic acid gives (−)-**11** with >98% ee[11] and 28% yield (74% based on recovered **11**) while co-crystallization with (*R*)-(−)-mandelic acid gives (+)-**11** with the same yield and enantiomeric purity. As such, both enantiomers are readily accessible.

Amino alcohol (−)-**11** is converted to (+)-**5** by nucleophilic catalysis (Scheme 3). Once the pivalamide is formed, its steric bulk prevents formation of the pivaloate and the reaction stops at (+)-**5**. For this reason, while acrylate (−)-**12a** can be formed by treatment with acryloyl chloride and $Et_3N$, attachment of larger dienophiles ((−)-**12b** and (−)-**12c**) requires more forcing conditions (Scheme 3).

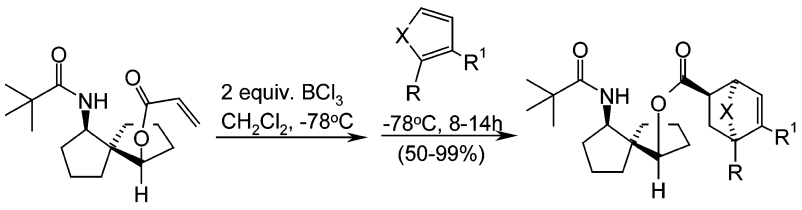
Acrylate (−)-**12a** was reacted with a variety of dienes in the presence of $BCl_3$ at −78°C (Scheme 4, Table 1, entries 1–6). The first equivalent of $BCl_3$ coordinated to the amide while a second equivalent activated the dienophile.[12] Frequently, the efficacy of a chiral auxiliary has been demonstrated only for the reaction between an acrylate (or doubly activated dienophile) and the highly reactive cyclopentadiene. Despite the steric bulk of (−)-**12a**, it reacts not only with cyclopentadiene but with several less reactive dienes (isoprene, furan, 1-vinylcyclopentene and 1-vinylcyclohexene) to provide adducts **13a**–**c**,**e** with high *endo* selectivity (>99:1) and high diastereoselectivity (>98% de). Only furan provided a poor mixture of *endo*:*exo* adducts (−)-**13e** (2:1). The only noticeable exception to the generally high diastereoselectivity is the reaction with 1-vinylcyclohexene, where the *endo* isomer (−)-**13f** is formed with high selectivity (*endo*:*exo* >99:1) but with lower de (85%). The reaction with 1-vinylcyclohexene gives access to a substituted decalin for which no asymmetric synthesis has been previously reported.[13] Similarly, the reaction with 1-vinylcyclopentene gave access to a substituted bicyclo[4.3.0]nonane, (−)-**13f**, that has only been reported in racemic form as the methyl ester derivative.[14] Unfortunately, partial migration of the double bond into the pentacycle to form an adduct with a tetrasubsituted double bond was also observed (see **22**,[14,15] Table 2). The absolute and rela-




**Scheme 2.**




**Scheme 3.**




**Scheme 4.**

**Table 1.** Diels–Alder reaction of chiral dienophiles (−)-**12a**, (−)-**12b** and (−)-**12c** with various dienes[a]

| | Diene | Product (yield)[b] | *endo*:*exo* | % de[c] |
|---|---|---|---|---|
| (−)-**12a** | Cyclopentadiene | (+)-**13a** (84%) | >99:1 | >98 |
| (−)-**12a** | Cyclohexadiene | (−)-**13b** (99%) | >99:1 | >98 |
| (−)-**12a** | Isoprene | (−)-**13c** (78%) | N/a | >98 |
| (−)-**12a** | Furan | (−)-**13d** (73%) | 2:1 | >98 (*endo*), >98 (*exo*) |
| (−)-**12a** | 1-Vinylcyclopentene | (−)-**13e** (94%) | >99[d]:1 | >98[d] |
| (−)-**12a** | 1-Vinylcyclohexene | (−)-**13f** (50% [98%]) | >99:1 | 85 |
| (−)-**12b** | Cyclopentadiene | (+)-**14** (63% [90%])[e] | 7:1[e] | 85 (*endo*)[e] |
| (−)-**12c** | Cyclopentadiene | (−)-**15** (64% [74%]) | 1:4 | 77 (*endo*), 79 (*exo*) |

[a] All reactions (except crotonate) were performed in $CH_2Cl_2$ at −78°C for 8–14 h using 2 equiv. $BCl_3$.
[b] Isolated yield. Yields in square brackets are based on recovered dienophile.
[c] The de value was determined from the relative integration in the 400 MHz $^1H$ NMR spectra. In all cases, high temperature reactions were also performed to ensure that all potential products could be distinguished.
[d] 3:1 mixture of *endo* product: product in which double bond has migrated to be tetrasubstituted.
[e] The crotonate reaction did not proceed at −78°C; results are for reaction at −23°C.

tive stereochemistry and the regiochemistry of the adducts (−)-**13e** and (−)-**13f** were determined by X-ray crystallography (Fig. 1).[16]

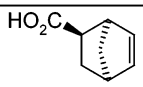
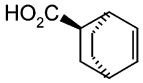
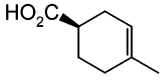
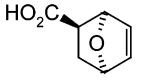
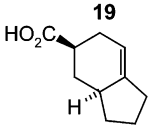
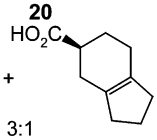
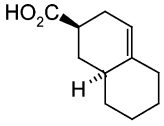
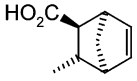
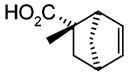
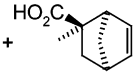
Crotonates are less reactive than acrylates and (−)-**12b** does not react at all with cyclopentadiene at −78°C. Warming to −23°C, however, gives Diels–Alder products with a 7:1 *endo*:*exo* ratio and 85% de for the *endo* isomer (+)-**14** (Scheme 5, Table 1). Methacrylates are also less reactive than acrylates; however, (−)-**12c** did react with cyclopentadiene at −78°C given a longer reaction time (Scheme 5). Because the $CH_3$ and $CH_2$ groups are similar in size, methacrylates generally give atrocious diastereoselectivities due to free rotation, which continuously exchanges the positions of the two groups. As opposed to the other systems studied herein, the major product is the *exo* isomer (−)-**15** (carbonyl relative to the bridge), and it is formed with a respectable 79% de (Table 1).

Aside from excellent diastereocontrol, the main advantage of this auxiliary is its ease of removal. Treatment of adducts **13a**–**f**, (+)-**14** and (−)-**15** with NaOH in MeOH (80°C, 20 h) followed by a quench with 4N HCl gave the corresponding free carboxylic acids **16**–**26**[17–20] and allowed full recovery of auxiliary (+)-**5** (Table 2). No epimerization was observed at the stereogenic center α to the carboxylic acid, and no change in the *endo*:*exo* ratios was observed.

Interestingly, the diastereomer (1*R*,5*R*,6*R*)-6-pivalamido[4.4]spirononan-1-ol (+)-**5** gave predominantly *endo* adducts from the Diels–Alder reaction having the *R*-configuration α to the carboxylic acid. This is in contrast to the reaction of the diastereomeric (1*S*,5*R*,6*R*)-6-(pivalamido)spiro[4.4]nonan-1-ol (−)-**3**, which gave *endo* Diels–Alder adducts with *S*-configuration at the stereocenter α to the carboxylic acid.[7a] Thus, the same sense of chirality at the spiro and amido centers, but the differing stereochemistry at C-1, leads to products that are enantiomeric. Thus, only one enantiomer of (±)-**11** is needed from the resolution to allow the preparation of both enantiomers from the Diels–Alder reactions since (−)-**3** and (+)-**5** are readily interconverted (Scheme 1).

In conclusion, we have designed and synthesized an excellent chiral auxiliary (+)-**5** for use in the Diels–Alder reaction. Adducts are generally formed with excellent diastereo- and stereocontrol and are easily removed from the chiral auxiliary by saponification to provide the free carboxylic acids in excellent yields and the chiral auxiliary (+)-**5**. Auxiliary (+)-**5** is easily separated from the acids and reused. We are currently using enantiopure (−)-**11** as a chiral ligand in other Lewis acid-catalyzed reactions and the results will be reported in due course.

**Table 2.** Removal of chiral auxiliary from **13–15** to give chiral acids[a]

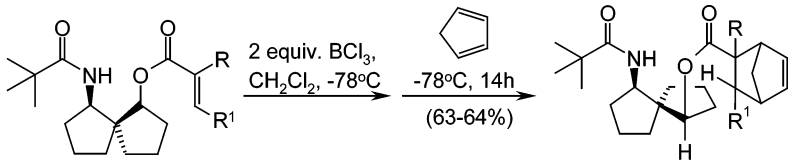
| SM (*endo*:*exo*) | Yield[b] | ee | $[\alpha]^{20}_D$ | Product(s) |
|---|---|---|---|---|
| (+)-**13a** (>99:1) | 92% | >98%[c,d] | +135 (1.1, 95% EtOH) (+144 (0.47, 95% EtOH))[17] |  (+)-**16** |
| (-)-**13b** (>99:1) | 93% | >98%[c,d] | +46 (0.53, MeOH) (+50.9 (0.45, MeOH))[18] |  (+)-**17** |
| (-)-**13c** (n/a) | 77% | >98%[d] | +77.8 (0.84, $CHCl_3$) (-74.6 (0.53, $CHCl_3$))[19] |  (+)-**18** |
| (-)-**13d** (2:1) | 72% | [e] | Inseparable mixture of isomers |  + exo isomer |
| (-)-**13e**[f] (>99:1) | 82% | Major isomer >98%[c,g] | +21.4 (1.07, $CHCl_3$) | **19**  + **20**  3:1 (+)-**21** **22** |
| (-)-**13f** (>99:1) | 73% | 85%[c,g] | +64.8 (0.77, $CHCl_3$) |  (+)-**23** |
| (+)-**14** (7:1) | 75% | 85% (*endo*)[c,d] | +97.4 (0.69, HPLC EtOH) (-151 (3.6, 95% EtOH))[20] |  (+)-**24** |
| (-)-**15** (1:4) | 46% | 77% (*endo*), 79% (*exo*)[c,d] | Inseparable mixture of isomers |  +  **25** **26** |

a) The auxiliary was cleaved by stirring overnight at 80°C in the minimum volume of MeOH with 5 M $NaOH_{(aq)}$.
b) Isolated yield.
c) No epimerization was observed by 400 MHz $^1$H NMR.
d) Absolute stereochemistry was assigned by comparing the sign of the specific rotation to that reported in the literature.
e) The acid had the same *endo*:*exo* ratio as the adduct and a negative specific rotation value. The two products were inseparable so their *ee* could not be determined.
f) Compound (-)-**13e** was a 3:1 mixture of double bond isomers.
g) The absolute and relative stereochemistry and the regiochemistry of (+)-**21** and (+)-**23** were determined from the X-ray crystal structure of the Diels-Alder adducts while still attached to the chiral auxiliary (+)-**5** (i.e. (-)-**13e** and (-)-**13f**).

## 3. Experimental procedures

### 3.1. Synthesis of alcohol 8

A flask equipped with a condenser was charged with Mg (24.2 g, 996 mmol), THF (750 ml) and catalytic $I_2$. Addition of 1,4-dibromobutane (41.8 g, 194 mmol) in THF (100 ml) over 30 min caused the red–brown colour to dissipate and the mixture to reflux. After heating under reflux for 24 h, δ-valerolactone (17.8 g, 178 mmol) in THF (100 ml) was added to the dark grey solution over 1 h. The resulting light grey suspension was heated under reflux for 5 h and then cooled to room temperature. The slurry was decanted off and cooled to 0°C, and the residual Mg was washed with water (200 ml) and EtOAc (200 ml) which was then added to quench the slurry. $HCl_{(aq)}$ (10%) was added until no cloudiness remained. Extraction with EtOAc (3×300 ml), washing with saturated $NaHCO_{3(aq)}$ (200 ml) then brine (200 ml), drying over $MgSO_4$ and concentration in vacuo gave the diol as a tan liquid which was used without purification. It was dissolved in DMSO (400 ml) and water (80 ml). Oxalic acid dihydrate (22.6 g, 179 mmol) was added, and the solution was stirred at 120°C for 2 h. After cooling to room temperature, the solution was extracted with $Et_2O$ (4×150 ml), washed with brine (3×200 ml), dried over $MgSO_4$ and concentrated in vacuo to give a tan liquid. Distillation by Kugelrohr (0.25 Torr, 70°C) gave **8** (17.8 g, 127 mmol, 71.4%) as a colourless liquid: bp 50°C/0.05 Torr (air bath); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 5.38 (m, 1H), 3.66 (t, $J=6.4$ Hz, 2H), 2.36–1.38 (m, 12H). diol: bp 110°C/0.1 Torr (air bath); lit.[4] bp 88–90°C/0.01 Torr; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 3.68 (t, $J=6.3$ Hz, 2H), 1.95–1.40 (m, 14H).




(-)-**12b**: R=H, R¹=Me
(-)-**12c**: R=Me, R¹=H

(+)-**14**: R=H, R¹=Me
(-)-**15**: R=Me, R¹=H

**Scheme 5.**

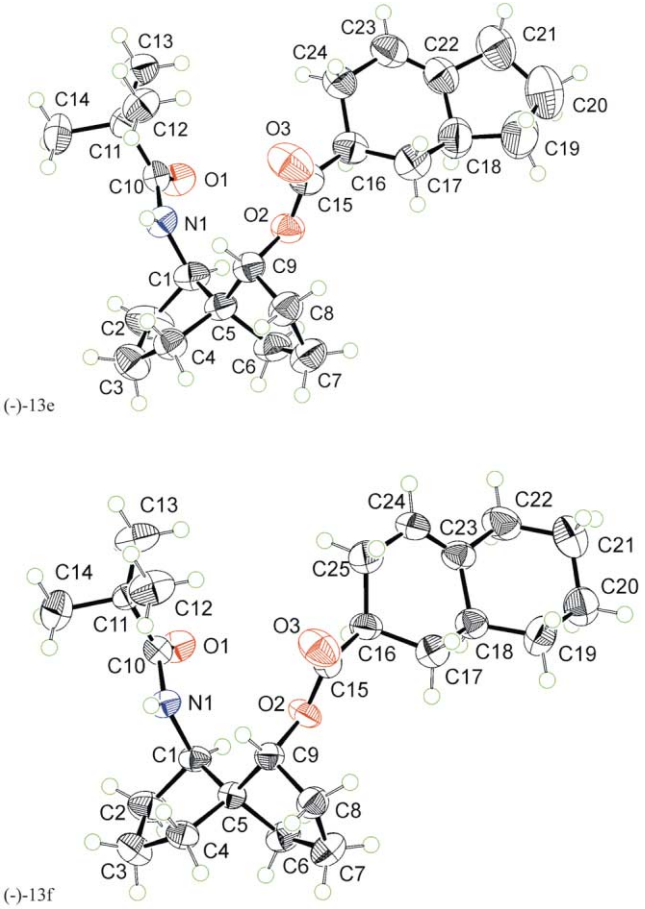



**Figure 1.** ORTEPs of Diels–Alder adducts (–)-**13e** and (–)-**13f**.

### 3.2. Synthesis of oxime 9

To a pale yellow suspension of Dess–Martin periodinane (44.2 g, 104 mmol) in $CH_2Cl_2$ (300 ml) was added **8** (11.1 g, 78.9 mmol) in $CH_2Cl_2$ (100 ml). After stirring for 1 h, the mixture was thick with white precipitate. It was poured into $Et_2O$ (350 ml), saturated $Na_2CO_{3(aq)}$ (350 ml) and saturated $Na_2S_2O_{3(aq)}$ (350 ml) and stirred for 1 h. The tan aqueous phase was extracted with $Et_2O$ (2×300 ml), and the combined organics were washed with brine (200 ml), dried over $MgSO_4$ and concentrated in vacuo to give the aldehyde as a light yellow liquid which was used without purification. It was dissolved in $Et_2O$ (250 ml) and added to an aqueous solution of $Na_2CO_3$ (25.2 g, 238 mmol) and $NH_2OH{\cdot}HCl$ (14.0 g, 201 mmol). After vigorous stirring for 15 h, the aqueous phase was extracted with $Et_2O$ (2×200 ml), and the combined organics were washed with brine (200 ml), dried over $MgSO_4$ and concentrated in vacuo. Distillation by Kugelrohr (0.2 Torr, 85°C) gave **9**[1] (11.4 g, 74.3 mmol, 94.1%) as a waxy white solid (mixture of *E*- and *Z*-isomers): bp 60°C/0.2 Torr (air bath); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.44 (t, $J$=6.1 Hz, 0.5H), 6.74 (t, $J$=5.5 Hz, 0.5H), 5.36 (m, 1H), 2.48–2.06 (m, 8H), 1.86 (p, $J$=7.4 Hz, 2H), 1.66 (p, $J$=7.5 Hz, 2H). aldehyde: bp 90°C/20 Torr (air bath); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 9.78 (t, $J$=1.7 Hz, 1H), 5.36 (m, 1H), 2.44 (td, $J$=7.3, 1.7 Hz, 2H), 2.38–2.06 (m, 6H), 1.96–1.72 (m, 4H).

### 3.3. Synthesis of 2-isoxazoline (±)-10

$NaOCl_{(aq)}$ (5.25%, 20.0 ml) was added to a solution of **9** (850 mg, 5.55 mmol) in $CH_2Cl_2$ (25 ml) and stirred vigorously for 15 h. Extraction with $CH_2Cl_2$ (3×25 ml), washing with brine (20 ml), drying over $MgSO_4$ and concentration in vacuo followed by flash chromatography (silica, 9:1 hexanes:EtOAc) gave (±)-**10** as a pale yellow liquid (430 mg, 2.84 mmol, 51.2%): bp 85°C/20 Torr; IR (film) $\nu_{max}$ 2955, 2866, 1736, 1645, 1601, 1547, 1449, 1435, 1328, 1304, 1256, 1215, 1023, 952, 912, 889, 872, 833 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.75 (m, 1H), 2.45–2.37 (m, 2H), 2.20–1.39 (m, 10H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 171.1 (C), 91.4 (CH), 71.0 (C), 37.9 ($CH_2$), 34.9 ($CH_2$), 34.2 ($CH_2$), 25.6 ($CH_2$), 24.2 ($CH_2$), 20.2 ($CH_2$); MS: $m/z$ 151 (67, $M^+$), 134 (23), 122 (39), 95 (21), 94 (32), 93 (87), 91 (36), 83 (22), 80 (33), 79 (100), 77 (33), 67 (62), 55 (45), 53 (25), 41 (44), 39 (40); HRMS calcd for $C_9H_{13}NO$ 151.09971, found 151.09936.

### 3.4. Synthesis of amino alcohol (±)-11

(±)-**10** (1.13 g, 7.45 mmol) in THF (15 ml) was added to a suspension of $LiAlH_4$ (380 mg, 10.0 mmol) in THF (15 ml) at 0°C, warmed to 22°C and stirred for 15 h. The grey suspension was cooled to 0°C and quenched with $NaOH_{(aq)}$ (10%, 5 ml). Upon warming to room temperature, enough $NaOH_{(aq)}$ (10%, ~100 ml) was added to dissolve Al salts. Extraction with $Et_2O$ (3×75 ml), washing with brine (75 ml), drying over $Na_2SO_4$ and concentration in vacuo gave (±)-**11** as a white waxy solid (1.00 g, 6.43 mmol, 86.3%): bp 45°C/0.2 Torr; IR (film) $\nu_{max}$ 3280, 2953, 2865, 1575, 1455, 1377, 1328, 1306, 1157, 1092, 1048, 996, 948, 907, 818 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 4.12–4.02 (m, 1H), 3.28 (t, $J$=6.3 Hz, 1H), 2.83 (br s, 3H), 2.14–1.21 (m, 12H); $^{13}$C

NMR (50 MHz, $CDCl_3$): $\delta$ 79.0 (CH), 59.3 (CH), 56.1 (C), 35.3 ($CH_2$), 35.2 ($CH_2$), 35.1 ($CH_2$), 33.3 ($CH_2$), 21.1 ($CH_2$), 20.9 ($CH_2$); MS: $m/z$ 155 (1, $M^+$), 136 (40), 120 (22), 108 (30), 95 (29), 94 (30), 93 (43), 91 (64), 82 (40), 80 (38), 79 (100), 77 (24), 67 (38), 57 (69), 56 (26), 45 (31), 43 (42), 42 (23), 34 (40); HRMS calcd for $C_9H_{17}NO$ 155.13101, found 155.13257.

### 3.5. Resolution of amino alcohol 11

(±)-**11** (991 mg, 6.38 mmol) was dissolved in MeCN (40 ml). (+)-Mandelic acid (482 mg, 3.17 mmol) was dissolved in MeCN (40 ml). The two solutions were combined, swirled gently and allowed to sit for 12 h. The resulting fluffy white needles were filtered off. These crystals were added to $NaOH_{(aq)}$ (10%, 25 ml). Extraction with $Et_2O$ (3×50 ml), drying over $Na_2SO_4$ and concentration in vacuo gave (−)-**11** (277 mg, 1.78 mmol, 27.9%, >99% ee). The filtrate was concentrated in vacuo, and the resulting light yellow oil was added to $NaOH_{(aq)}$ (10%, 25 ml). Extraction with $Et_2O$ (3×50 ml), drying over $Na_2SO_4$ and concentration in vacuo gave (+)-**11** (618 mg, 3.98 mmol, 62.3%, 70–80% ee). This optically enriched **11** was dissolved in MeCN (20 ml) and added to a solution of (−)-mandelic acid (509 mg, 3.35 mmol) in MeCN (20 ml). Fluffy white needles formed almost immediately and, after sitting for 12 h, the crystals were filtered off. Addition of $NaOH_{(aq)}$ (10%, 15 ml), extraction with $Et_2O$ (3×25 ml), drying over $Na_2SO_4$ and concentration in vacuo gave (+)-**11** (275 mg, 1.77 mmol, 27.8%, >99% ee) $[\alpha]_D^{23}$ +79.3 ($c$ 2.0, $CHCl_3$). Work-up of the filtrate as described above gave recovery of **11** (282 mg, 1.82 mmol, 28.5%).

### 3.6. Synthesis of amido alcohol (+)-5

(−)-**11** (950 mg, 6.12 mmol) and pyridine (5.0 ml, 62 mmol) were dissolved in $CH_2Cl_2$ (40 ml). Trimethylacetic anhydride (4.0 ml, 20 mmol) was added, and the reaction was stirred at room temperature for 1 day. The resulting light yellow solution was quenched with water (10 ml) then $HCl_{(aq)}$ (10%, 20 ml), extracted with $CH_2Cl_2$ (3×50 ml), washed with brine (50 ml) and dried over $MgSO_4$. Concentration in vacuo followed by flash chromatography (silica, 7:3 hexanes:EtOAc) gave (+)-**5** (1.42 g, 5.94 mmol, 97.0%) as a white solid: mp 101–103°C; $[\alpha]_D^{20}$ +5.2 ($c$ 0.46, $CHCl_3$); IR (film) $\nu_{max}$ 3346, 2960, 2874, 1634, 1531, 1459, 1361, 1332, 1223, 1099, 1043, 1021, 914, 677 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 5.89 (br d, 1H), 4.01 (t, $J$=6.5 Hz, 1H), 3.67 (bs, 1H), 2.1–1.0 (m, 13H), 1.21 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 179.5 (C), 77.6 (CH), 60.8 (C), 56.5 (CH), 38.7 (C), 32.4 ($CH_2$), 32.3 ($CH_2$), 32.0 ($CH_2$), 30.9 ($CH_2$), 27.6 ($CH_3$), 20.6 ($CH_2$), 20.0 ($CH_2$); MS: $m/z$ 239 (4, $M^+$), 121 (20), 120 (37), 102 (100), 57 (38); HRMS calcd for $C_{14}H_{25}NO_2$ 239.18853, found 239.18835; analysis calcd for $C_{14}H_{25}NO_2$ C, 70.25; H, 10.53; N, 5.85, found: C, 70.19; H, 10.83; N, 5.82%.

### 3.7. Synthesis of amido acrylate (−)-12a

(+)-**5** (1.50 g, 6.27 mmol) and $Et_3N$ (2.60 ml, 18.7 mmol) were dissolved in dry $CH_2Cl_2$ (60 ml) and cooled to 0°C. Acryloyl chloride (1.00 ml, 12.3 mmol) was added, and the solution was allowed to warm to room temperature and stirred for 18 h. The resulting gold solution was quenched with water (10 ml) then $HCl_{(aq)}$ (4 M, 50 ml), extracted with $CH_2Cl_2$ (3×50 ml), washed with saturated $Na_2CO_{3(aq)}$ (50 ml) and dried over $MgSO_4$. Concentration in vacuo followed by flash chromatography (silica, 5:1 hexanes:EtOAc) gave (−)-**12a** (1.37 g, 4.67 mmol, 74.5%) as a fluffy white solid: mp 126–127°C; $[\alpha]_D^{22}$ −56.9 ($c$ 0.91, $CHCl_3$); IR (film) $\nu_{max}$ 3470, 3343, 2965, 2871, 1721, 1638, 1530, 1407, 1367, 1296, 1275, 1203, 1102, 1050, 984, 911, 811, 733, 647 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 6.40 (dd, $J$= 17.2, 1.6 Hz, 1H), 6.10 (dd, $J$=17.3, 10.2 Hz, 1H), 5.97 (br d, 1H), 5.83 (dd, $J$=10.2, 1.7 Hz, 1H), 5.12–5.07 (m, 1H), 4.30–4.19 (m, 1H), 2.15–1.45 (m, 12H), 1.14 (s, 9H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 177.3 (C), 165.5 (C), 131.0 ($CH_2$), 128.5 (CH), 81.4 (CH), 56.4 (CH), 56.1 (C), 38.6 (C), 35.0 ($CH_2$), 34.9 ($CH_2$), 32.2 ($CH_2$), 31.9 ($CH_2$), 27.5 ($CH_3$), 21.0 ($CH_2$), 20.3 ($CH_2$); MS: $m/z$ 293 (4, $M^+$), 238 (12), 208 (32), 121 (57), 120 (100), 102 (67), 57 (79); HRMS calcd for $C_{17}H_{27}NO_3$ 293.19909, found 293.19849; anal. calcd for $C_{17}H_{27}NO_3$ C, 69.59; H, 9.28; N, 4.77; found: C, 69.65; H, 9.01; N, 4.77%.

### 3.8. Synthesis of amido-crotonate (−)-12b

(+)-**5** (525 mg, 2.19 mmol) and LHMDS·$OEt_2$ (1.11 g, 4.60 mmol) were dissolved in THF (20 ml) and stirred for 1 h to give a gold suspension. Crotonyl chloride (450 μl, 4.70 mmol) was added, and the solution was stirred for 16 h. The resulting gold solution was quenched with water (10 ml) then $HCl_{(aq)}$ (4 M, 30 ml), extracted with $CH_2Cl_2$ (3×30 ml), washed with saturated $Na_2CO_{3(aq)}$ (30 ml) and dried over $MgSO_4$. Concentration in vacuo followed by flash chromatography (silica, 5:1 hexanes:EtOAc) gave (−)-**12b** (496 mg, 1.61 mmol, 73.7%) as a white solid: mp 113–114°C; $[\alpha]_D^{20}$ −50.8 ($c$ 1.07, $CHCl_3$); IR (film) $\nu_{max}$ 3334, 2964, 2950, 2867, 1715, 1630, 1535, 1442, 1309, 1186 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.96 (dq, $J$=15.5, 6.9 Hz, 1H), 6.05 (br d, 1H), 5.82 (dd, $J$=15.5, 1.7 Hz, 1H), 5.08 (dd, $J$=5.6, 2.2 Hz, 1H), 4.23–4.18 (m, 1H), 2.15–1.45 (m, 15H), 1.14 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 177.6 (C), 165.8 (C), 145.3 (CH), 122.7 (CH), 81.0 (CH), 56.6 (CH), 55.7 (C), 38.6 (C), 35.2 ($CH_2$), 35.1 ($CH_2$), 32.3 ($CH_2$), 31.8 ($CH_2$), 27.5 ($CH_3$), 21.1 ($CH_2$), 20.3 ($CH_2$), 18.0 ($CH_3$); MS: $m/z$ 308 (1, $[M+1]^+$), 238 (19), 222 (67), 221 (54), 179 (38), 136 (65), 121 (73), 120 (100), 117 (75), 102 (96), 91 (92), 79 (84), 57 (77), 41 (80); HRMS calcd for $C_{18}H_{29}NO_3$ 307.21474, found 307.21301; anal. calcd for $C_{18}H_{29}NO_3$ C, 70.32; H, 9.51; N, 4.56; found: C, 70.11; H, 9.81; N, 4.54%.

### 3.9. Synthesis of amido-methacrylate (−)-12c

(+)-**5** (515 mg, 2.15 mmol) and LHMDS·$OEt_2$ (1.11 g, 4.60 mmol) were dissolved in THF (20 ml) and stirred for 1 h to give a gold suspension. Methacryloyl chloride (450 μl, 4.61 mmol) was added, and the solution was stirred for 16 h. The resulting yellow solution was quenched with water (10 ml) then $HCl_{(aq)}$ (4 M, 30 ml),

extracted with $CH_2Cl_2$ (3×30 ml), washed with saturated $Na_2CO_{3(aq)}$ (30 ml) and dried over $MgSO_4$. Concentration in vacuo followed by flash chromatography (silica, 5:1 hexanes:EtOAc) gave (−)-**12c** (510 mg, 1.66 mmol, 77.2%) as a white solid: mp 89°C; $[\alpha]_D^{20}$ −75.8 (*c* 0.87, $CHCl_3$); IR (film) $\nu_{max}$ 3353, 2966, 2870, 1702, 1631, 1529, 1319, 1162, 937 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 6.06 (br s, 1H), 5.84 (br d, 1H), 5.56 (t, $J=1.9$ Hz, 1H), 5.08 (br d, 1H), 4.29–4.18 (m, 1H), 2.12–1.50 (m, 15H), 1.12 (s, 9H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 177.2 (C), 166.8 (C), 136.5 (C), 125.5 ($CH_2$), 81.3 (CH), 56.7 (CH), 56.4 (C), 38.6 (C), 35.3 ($CH_2$), 34.6 ($CH_2$), 32.2 ($CH_2$), 32.0 ($CH_2$), 27.5 ($CH_3$), 20.8 ($CH_2$), 20.5 ($CH_2$), 18.3 ($CH_3$); MS: *m*/*z* 307 (1, $M^+$), 238 (7), 222 (35), 121 (68), 120 (100), 102 (63), 57 (45); HRMS calcd for $C_{18}H_{29}NO_3$ 307.21474, found 307.21473; anal. calcd for $C_{18}H_{29}NO_3$ C, 70.32; H, 9.51; N, 4.56; found: C, 70.06; H, 9.68; N, 4.51%.

### 3.10. Typical procedure for the Diels–Alder reaction

A flask containing (−)-**12a** (100 mg, 0.342 mmol) and 4 Å molecular sieves (140 mg) was flushed with dry $N_2$ for 5 min. Dry $CH_2Cl_2$ (6 ml) was added, and the solution was cooled to −78°C before adding $BCl_3$ (1.0 m in $CH_2Cl_2$, 680 μl, 0.68 mmol). After stirring for 30 min, cyclohexadiene (160 μl, 1.68 mmol, pre-cooled to 0°C) was added down the side of the flask. After stirring for 8 h, the light yellow solution was filtered through a silica plug (1.8 g, pre-wetted with $CH_2Cl_2$) and flushed through with $Et_2O$. Concentration in vacuo followed by flash chromatography (silica, 4:1 hexanes:EtOAc) gave (−)-**13b** (127 mg, 0.340 mmol, 99.6%) as a white solid: mp 98–99°C; $[\alpha]_D^{23}$ −21.8 (*c* 0.95, $CHCl_3$); IR (film) $\nu_{max}$ 3465, 3442, 3385, 2948, 2868, 1727, 1651, 1511, 1365, 1320, 1238, 1200, 1103, 1052, 704 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.29 (t, $J=7.5$ Hz, 1H), 6.16 (t, $J=7.3$ Hz, 1H), 6.05 (br d, 1H), 5.00–4.95 (m, 1H), 4.18–4.11 (m, 1H), 2.88 (br s, 1H), 2.59 (br s, 2H), 2.05–1.90 (m, 2H), 1.8–1.2 (m, 16H), 1.17 (s, 9H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 177.4 (C), 174.5 (C), 135.0 (CH), 131.4 (CH), 81.0 (CH), 56.7 (CH), 55.7 (C), 43.2 (CH), 38.7 (C), 35.1 ($CH_2$), 35.0 ($CH_2$), 32.33 (CH), 32.29 ($CH_2$), 31.7 ($CH_2$), 30.2 ($CH_2$), 29.3 (CH), 27.6 ($CH_3$), 25.4 ($CH_2$), 24.2 ($CH_2$), 21.0 ($CH_2$), 20.3 ($CH_2$); MS: *m*/*z* 373 (12, $M^+$), 288 (31), 238 (28), 222 (78), 121 (79), 120 (100), 102 (81), 79 (52), 57 (47); HRMS calcd for $C_{23}H_{35}NO_3$ 373.26169, found 373.26069; anal. calcd for $C_{23}H_{35}NO_3$ C, 73.96; H, 9.44; N, 3.75; found: C, 73.42; H, 9.64; N, 3.74%.

### 3.11. Typical procedure for removal of the chiral auxiliary

$NaOH_{(aq)}$ (5 M, 15 ml) was added to a solution of (−)-**13b** (74.1 mg, 0.198 mmol) in MeOH (4.5 ml). After stirring at 80°C for 20 h, cooling to room temperature and removal of MeOH in vacuo, the reaction was cooled to 0°C and quenched with $HCl_{(aq)}$ (4 M) until the solution reached pH 2. Extraction with EtOAc (3×50 ml), drying over $MgSO_4$ and concentration in vacuo followed by flash chromatography (silica, 4:1 hexanes:EtOAc) gave (+)-**17** (28.1 mg, 0.185 mmol, 93.2%) as a white solid then (+)-**5** (34.4 mg, 0.144 mmol, 72.6%) as a white solid. (+)-**17**: mp 39–40°C; lit.[21] mp 46–47°C; $[\alpha]_D^{19}$ +46 (*c* 0.53, MeOH); lit.[18] $[\alpha]_D^{19}$ +50.9 (MeOH); $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 10.3 (br s, 1H), 6.40–6.27 (m, 1H), 6.25–6.13 (m, 1H), 3.03–2.93 (m, 1H), 2.75–2.55 (m, 2H), 1.87–1.15 (m, 6H).

## Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) and University of Calgary for financial support. S.M.L. gratefully acknowledges receipt of a NSERC scholarship and Ralph Steinhauer Award of Distinction from the Alberta Heritage Foundation.

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11. Measurement of % ee was achieved by chiral GC of the pivalamido alcohol derivative **5** using a Chiraldex-B-PM, 50 m×0.25 mm capillary column isothermally at 160°C. Absolute stereochemistry of **5** (and hence **11**) was determined by comparison of retention time to that of (+)-**5** prepared via our previously reported route to **3**[7a] (see Scheme 1).
12. The site of coordination of the $BCl_3$ was determined by a 400 MHz $^1H$ NMR low temperature experiment (−78°C) in which (−)-**12a** was dissolved in $CD_2Cl_2$ followed by four successive additions of 0.5 equiv. $BCl_3$.
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16. X-Ray crystallographic analysis of **13e** and **13f** was performed by Dr. M. Parvez at the University of Calgary. See the supporting information for the ORTEP. CCDC 190144 and 190145 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html. Compound **13e**: tetragonal $P4_3$; $a=11.2730(9)$, $c=18.3100(11)$, $V=2326.8(3)$ Å$^3$; $Z=4$; $R=0.047$; $wR=0.114$; Compound **13f**: tetragonal $P4_3$; $a=11.5142(5)$, $c=18.0266(13)$ Å, $V=2389.9(2)$ Å$^3$; $Z=4$; $R=0.063$; $wR=0.117$.
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