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A bicyclo[3.1.1]heptano[4,3-*c*]pyrazole derived chiral auxiliary for dipolar cycloadditions

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Received 10 March 2005; accepted 20 April 2005
Available online 23 May 2005

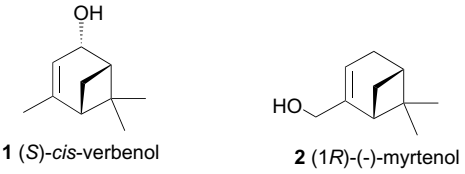
Abstract—Starting form naturally occurring (*S*)-*cis*-verbenol **1** and (1*R*)-(−)-myrtenol **2**, we synthesised enantiopure bicyclo[3.1.1]heptano[4,3-*c*]pyrazole derivatives **7** and **8** via a stereoselective nitrilimine cycloaddition as the key step. The effectiveness of the above skeleton as a new chiral auxiliary was evaluated towards the 1,3-dipolar cycloadditions of nitrile oxides and nitrilimines. Basic hydrolysis of the major cycloadducts gave enantiopure 5-carboxy-4,5-dihydroisoxazole (*S*)-(+)-**19** and 5-carboxy-4,5-dihydropyrazole (*S*)-(+)-**20**, respectively, which are of potential interest as chiral building blocks.

1. Introduction

For many decades the chiral pool has been the main source for effective chiral auxiliaries.[1] Due to their marked structural rigidity, terpene-based chiral reagents appear to be promising candidates for this role; however they have found limited synthetic applications due to their inherent lack of functionality.[1] This problem can be circumvented by suitable synthetic design of the starting natural compounds;[2] furthermore, it is well known that sterically demanding chiral auxiliaries can be built on bicyclic or polycyclic ring systems.[3] Recently, we have shown that naturally occurring oxygenated monoterpenes,[4] namely (*S*)-*cis*-verbenol **1** and (1*R*)-(−)-myrtenol **2**, are valuable starting materials for the stereoselective synthesis of the bicyclo[3.1.1]heptano[4,3-*c*]pyrazole skeleton in its enantiopure form.[5] Herein, we report the effectiveness of the above skeleton as a new chiral auxiliary for the 1,3-dipolar cycloadditions of *N*-(4-methyl)phenyl-*C*-methoxycarbonyl nitrilimine and benzonitrile oxide (Fig. 1).

2. Results and discussion

As is described in Scheme 1, novel tricyclic derivatives **7** and **8** were obtained in enantiopure form following a two-step sequence from (*S*)-*cis*-verbenol **1** and (1*R*)-(−)-myrtenol **2**, respectively. Fully regio- and stereoselective cycloaddition of nitrilimine **4**[6] onto both **1** and **2** gave carbinol intermediates **5** and **6**, which were submitted to esterification with acryloyl chloride under standard conditions. Structures **7** and **8** rely upon analytical and spectral data, while their absolute configurations were assigned unambiguously upon NOE experiments. In particular, NOE enhancement of H_A after irradiation of H_B (Fig. 2) is in strong agreement with that of similar bicyclo[3.1.1]heptano[4,3-*c*]pyrazoles[5] and is fully consistent with the depicted stereochemical arrangement.



1 (*S*)-*cis*-verbenol **2** (1*R*)-(-)-myrtenol

Figure 1.

With compounds **7** and **8** in hand, we were able to carry out an investigation to assess their suitability as chiral auxiliaries in promoting asymmetric reactions. Stereoselective benzonitrile oxide cycloaddition has often been exploited as a versatile synthetic tool for building up complex molecules.[7] On the other hand, research on stereoselective nitrilimine cycloadditions are still in their infancy[8] and further data could be useful. As a result, both kinds of nitrilium betaines seemed to be reasonable candidates as 'test reactants' for a new chiral auxiliary.

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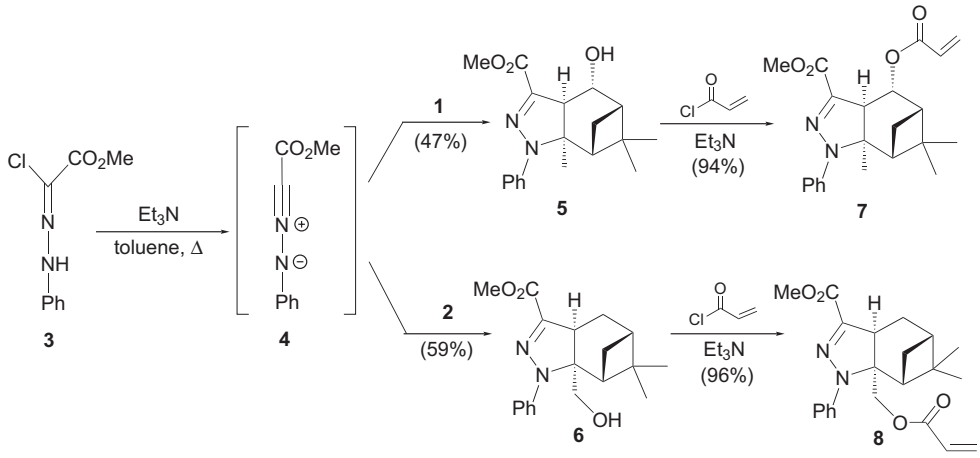
doi:10.1016/j.tetasy.2005.04.014



Scheme 1.

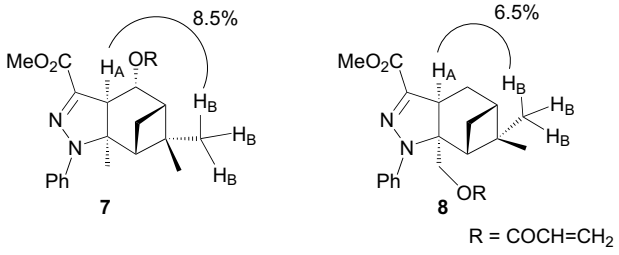
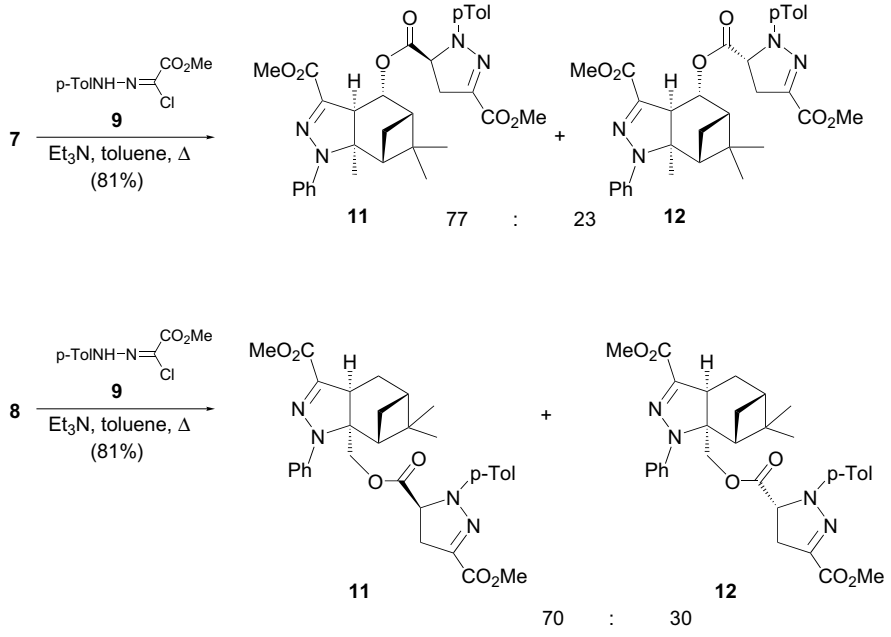


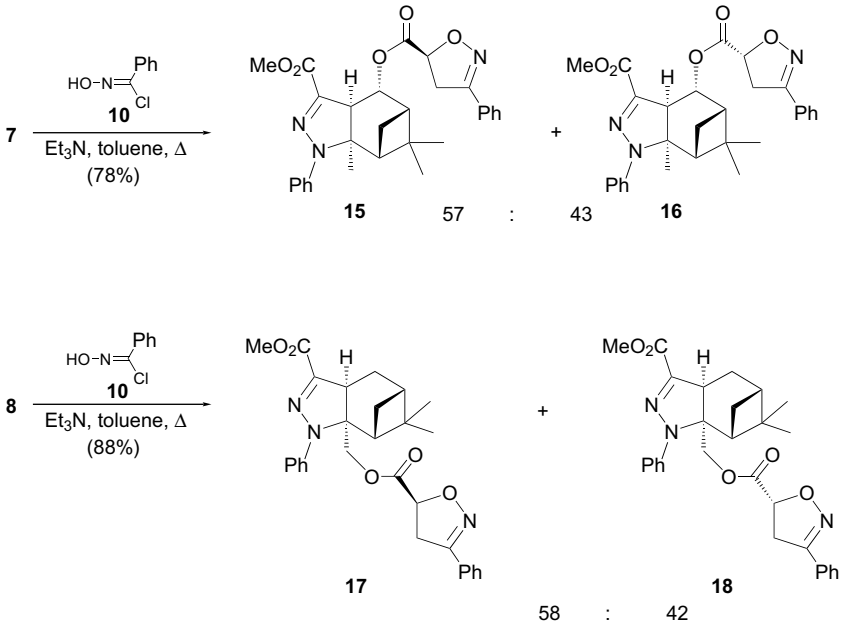
Figure 2.

The behaviour of compounds **7** and **8** towards *N*-(4-methyl)phenyl-*C*-methoxycarbonyl nitrilimine is depicted in Scheme 2. The dipolar intermediate, which was generated in situ from the corresponding hydrazonoyl chloride **9**,[9] underwent fully regioselective cycloaddition to the 5-substituted-4,5-dihydropyrazoles **11**–**14**. Spectroscopic data of the latter products (^{1}H NMR) are in full agreement with those of 5-substituted-4,5-dihydropyrazoles.[10] Major cycloadducts **11** and **13** were obtained chemically and enantiomerically pure through silica gel column chromatography, in good isolated yields. The absolute configuration of the newly formed stereocentre of major diastereoisomers **11** and **13** was determined by means of chemical correlation experiments. Basic hydrolysis of both **11** and **13** gave the same, known, 3,5-dicarboxy-4,5-dihydropyrazole (*S*)-(+)-**19**[8b] (Scheme 4) and allowed recovery of the chiral auxiliary. As far as the cycloaddition diastereoselectivity is concerned, the values 70:30 and 77:23 parallel those obtained with well-established acrylamide-type chiral auxiliaries such as Evan's oxazolidinone or Oppolzer's camphorsultam.[8b]

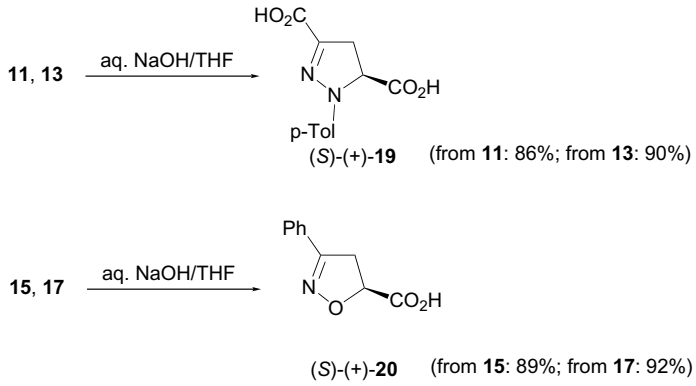
Scheme 3 illustrates the behaviour of compounds **7** and **8** towards benzonitrile oxide, which was generated in



Scheme 2.



Scheme 3.



Scheme 4.

situ from the corresponding chloroxime **10**.[11] Chromatographic treatment of cycloaddition mixtures afforded enantiopure major diastereoisomers **15** and **17** with good isolation yields. The absolute configuration of the isoxazoline at the 5-position of the major cycloadducts **15** and **17** was determined by means of chemical correlation experiments; basic hydrolysis of these cycloadducts gave the same, known, 3-phenyl-5-carboxy-4,5-dihydroisoxazole (*S*)-(+)-**20**[12] (Scheme 4). Although nitrile oxide cycloadditions were completely regioselective, their diastereoselectivity was quite disappointing (57:43 and 58: 42). This result, however, is not entirely surprising in light of the low diastereoselectivity usually involved in the cycloaddition between nitrile oxides and substituted bornyl crotonates.[13]

3. Conclusions

Notwithstanding their structural rigidity, acriloyl derivatives **7** and **8** were able to induce a moderate degree of stereoselection only in the case of nitrilimine cycloaddition. However, the displacement of the chiral auxiliaries from the cycloadducts and the recovery of enantiopure materials occurred easily and with good overall yields. Finally, our approach constitutes a facile four-step synthesis to the enantiopure small heterocycles (*S*)-(+)-**19** and (*S*)-(+)-**20**, which are of potential interest as chiral building blocks.

4. Experimental

Melting points were determined with a Büchi apparatus in open tubes and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H NMR (300 MHz) spectra were taken with a Bruker AMX 300 instrument (in $CDCl_3$ solutions at room temperature). Chemical shifts are given as parts per million from tetramethylsilane and *J* values are given in hertz. NOE experiments were performed by setting the following parameters: relaxation delay (d1) 2 s, irradiation power (dl2) 74 dB, and total irradiation time (for

each signal) 1.8 s. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter at the sodium D-line. Compounds **1** and **2** were used as purchased from Aldrich. Compounds **3**,[6] **9**[9] and **10**[11] were prepared according to the literature procedures.

4.1. Cycloaddition between hydrazonoyl chloride 3 and pinane derivatives 1 and 2

A solution of hydrazonoyl chloride **3** (0.53 g, 2.5 mmol) and the appropriate pinane derivative **1** or **2** (0.26 g, 1.7 mmol) in dry toluene (25 mL) was treated with triethylamine (1.26 g, 12.5 mmol) and refluxed for 48 h. The crude was evaporated under reduced pressure and the residue chromatographed on a silica gel column with ethyl acetate–hexane–dichloromethane 10:2:1. The first fractions contained the starting pinane derivative **1** or **2** in a 10–15% amount, followed by decomposition products of hydrazonoyl chloride **3**. Further elution gave cycloadducts **5** and **6**.

4.1.1. Compound 5. 0.26 g, 47%. Pale yellow powder; mp 83 °C (from diisopropyl ether); $[\alpha]_D^{25} = -37.4$ (*c* 0.24, $CHCl_3$); IR (Nujol) 3460, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (3H, s), 1.36 (3H, s), 1.37 (3H, s), 2.10–2.60 (4H, m), 3.20 (1H, br s), 3.28 (1H, d, *J* 4.2), 3.89 (3H, s), 4.12 (1H, dd, *J* 10.4, 4.2), 7.1–7.3 (5H, m); MS *m*/*z* 328 (M^+). Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.53; H, 7.40; N, 8.57.

4.1.2. Compound 6. 0.33 g, 59%. Pale yellow powder; mp 96 °C (from diisopropyl ether); $[\alpha]_D^{25} = -65.4$ (*c* 0.31, $CHCl_3$); IR (Nujol) 3450, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (3H, s), 1.27 (3H, s), 1.80–2.50 (6H, m), 3.40 (1H, br s), 3.61 (1H, d, *J* 12.7), 3.72 (1H, dd, *J* 11.5, 5.1), 3.81 (3H, s), 3.87 (1H, d, *J* 12.7), 7.2–7.3 (5H, m); MS *m*/*z* 328 (M^+). Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.52; H, 7.34; N, 8.49.

4.2. Reaction between bicyclo[3.1.1]heptano[4,5-*c*]pyrazoles 5,6 and acriloyl chloride

A solution of **5** or **6** (0.33 g, 1.0 mmol) in dry toluene (12 mL) was treated with triethylamine (0.12 g, 1.2 mmol) and acriloyl chloride (0.11 g, 1.2 mmol) and refluxed for 30 h. The crude was evaporated under reduced pressure and the residue taken up with chloroform (25 mL). The mixture was filtered and the organic layer washed with 5% sodium hydrogencarbonate (2 × 20 mL), dried over sodium sulfate and evaporated. The residue was crystallized from diisopropyl ether affording pure acrylates **7** and **8**.

4.2.1. Compound 7. 0.36 g, 94%. White powder; mp 76 °C (from diisopropyl ether); $[\alpha]_D^{25} = -98.5$ (*c* 0.44, $CHCl_3$); IR (Nujol) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (3H, s), 1.38 (3H, s), 1.49 (3H, s), 2.25–2.60 (4H, m), 3.54 (1H, d, *J* 4.5), 3.85 (3H, s), 5.24 (1H, dd, *J* 11.0, 4.5), 5.86 (1H, dd, *J* 12.1, 2.2), 6.18 (1H, dd, *J* 18.6, 12.1), 6.47 (1H, dd, *J* 18.6, 2.2), 7.2–7.3 (5H, m); MS *m*/*z* 382 (M^+). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.13; H, 6.88; N, 7.36.

4.2.2. Compound 8. 0.37 g, 96%. White powder; mp 79 °C (from diisopropyl ether); $[\alpha]_D^{25} = -107.2$ (*c* 0.40, $CHCl_3$); IR (Nujol) 1735, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (3H, s), 1.25 (3H, s), 1.80–2.50 (6H, m), 3.70 (1H, dd, *J* 11.5, 5.0), 3.90 (3H, s), 4.21 (2H, AB, *J* 13.3), 5.74 (1H, dd, *J* 12.4, 2.1), 5.98 (1H, dd, *J* 18.2, 12.4), 6.27 (1H, dd, *J* 18.2, 2.1), 7.2–7.3 (5H, m); MS *m*/*z* 382 (M^+). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.06; H, 6.87; N, 7.28.

4.3. Cycloadditions between acrylates 7 and 8 and hydrazonoyl chloride 9

A solution of **7** or **8** (0.46 g, 1.2 mmol) and hydrazonoyl chloride **9** (0.34 g, 1.5 mmol) in dry toluene (12 mL) was treated with triethylamine (0.61 g, 6.0 mmol) and refluxed for 24 h. The crude was evaporated under reduced pressure and the residue was chromatographed on a silica gel column with hexane–ethyl acetate–dichloromethane 3:1:1. Major diastereoisomer **11** or **13** was eluted first, followed from minor **12** or **14**.

4.3.1. Compound 11. 0.43 g, 62%. Pale yellow powder; mp 111 °C (from diisopropyl ether); $[\alpha]_D^{25} = -48.8$ (*c* 0.22, $CHCl_3$,); IR (Nujol) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (3H, s), 1.34 (3H, s), 1.46 (3H, s), 2.25 (3H, s), 2.30–2.50 (4H, m), 3.28 (1H, dd, *J* 12.8, 7.4), 3.54 (1H, dd, *J* 12.8, 9.6), 3.71 (1H, d, *J* 4.5), 3.88 (3H, s), 3.92 (3H, s), 4.86 (1H, dd, *J* 9.6, 7.4), 5.12 (1H, dd, *J* 10.2, 4.5), 7.1–7.4 (9H, m); MS *m*/*z* 572 (M^+). Anal. Calcd for $C_{32}H_{36}N_4O_6$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.09; H, 6.30; N, 9.83.

4.3.2. Compound 12. 0.13 g, 19%. White powder; mp 89 °C (from diisopropyl ether); $[\alpha]_D^{25} = +16.3$ (*c* 0.30, $CHCl_3$); IR (Nujol) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (3H, s), 1.33 (3H, s), 1.40 (3H, s), 2.28 (3H, s), 2.30–2.50 (4H, m), 3.22 (1H, dd, *J* 12.8, 7.0), 3.50 (1H, dd, *J* 12.8, 9.4), 3.74 (1H, d, *J* 4.5), 3.85 (3H, s), 3.90 (3H, s), 4.90 (1H, dd, *J* 9.4, 7.0), 5.10 (1H, dd, *J* 10.2, 4.5), 7.1–7.4 (9H, m); MS *m*/*z* 572 (M^+). Anal. Calcd for $C_{32}H_{36}N_4O_6$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.10; H, 6.31; N, 9.84.

4.3.3. Compound 13. 0.30 g, 52%. White powder; mp 58 °C (from diisopropyl ether); $[\alpha]_D^{25} = -49.6$ (*c* 0.30, $CHCl_3$); IR (Nujol) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (3H, s), 1.28 (3H, s), 1.80–2.50 (6H, m), 2.28 (3H, s), 3.11 (1H, dd, *J* 12.6, 7.5), 3.44 (1H, dd, *J* 12.6, 9.5), 3.54 (1H, dd, *J* 11.3, 4.5), 3.84 (3H, s), 3.89 (3H, s), 3.93 (1H, d, *J* 12.5), 4.32 (1H, d, *J* 12.5), 4.83 (1H, dd, *J* 9.5, 7.5), 7.0–7.5 (9H, m); MS *m*/*z* 572 (M^+). Anal. Calcd for $C_{32}H_{36}N_4O_6$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.13; H, 6.36; N, 9.81.

4.3.4. Compound 14. 0.15 g, 22%. White powder; mp 79 °C (from diisopropyl ether); $[\alpha]_D^{25} = +17.5$ (*c* 0.11, $CHCl_3$); IR (Nujol) 1735, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (3H, s), 1.23 (3H, s), 1.80–2.50 (6H, m), 2.25 (3H, s), 3.17 (1H, dd, *J* 12.6, 7.5), 3.42 (1H, dd, *J* 12.6, 9.6), 3.54 (1H, dd, *J* 11.1, 4.5), 3.81 (3H, s), 3.90 (3H, s), 3.98 (1H, d, *J* 12.5), 4.30 (1H, d, *J* 12.5), 4.88 (1H, dd, *J* 9.6, 7.5), 7.0–7.5 (9H, m); MS *m*/*z* 572 (M^+).

Anal. Calcd for $C_{32}H_{36}N_4O_6$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.09; H, 6.31; N, 9.73.

4.4. Cycloadditions between acrylates 7 and 8 and benzaldehyde chloroxime 10

A solution of **7** or **8** (0.46 g, 1.2 mmol) and benzaldehyde chloroxime **10** (0.18 g, 1.2 mmol) in dry toluene (12 mL) was treated with triethylamine (0.20 g, 2.0 mmol) and refluxed for 36 h. The crude was evaporated under reduced pressure and the residue chromatographed on a silica gel column with hexane–ethyl acetate–dichloromethane 3:1:1. Major diastereoisomer **15** or **17** was eluted first, followed from minor **16** or **18**.

4.4.1. Compound 15. 0.26 g, 44%. Pale yellow powder; mp 94 °C (from diisopropyl ether); $[\alpha]_D^{25} = -32.5$ (*c* 0.44, $CHCl_3$); IR (Nujol) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3H, s), 1.31 (3H, s), 1.46 (3H, s), 2.20–2.50 (4H, m), 3.48 (1H, dd, *J* 12.0, 5.3), 3.74 (1H, dd, *J* 12.0, 9.2), 3.79 (3H, s), 4.00 (1H, d, *J* 4.5), 5.20–5.26 (2H, m), 7.0–7.4 (10H, m); MS *m*/*z* 501 (M^+). Anal. Calcd for $C_{29}H_{31}N_3O_5$: C, 69.44; H, 6.23; N, 8.38. Found: C, 69.48; H, 6.25; N, 8.43.

4.4.2. Compound 16. 0.20 g, 34%. Pale yellow powder; mp 116 °C (from diisopropyl ether); $[\alpha]_D^{25} = +13.5$ (*c* 0.18, $CHCl_3$); IR (Nujol) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (3H, s), 1.33 (3H, s), 1.43 (3H, s), 2.20–2.50 (4H, m), 3.40 (1H, dd, *J* 12.0, 5.4), 3.74 (1H, dd, *J* 12.0, 9.2), 3.80 (3H, s), 3.95 (1H, d, *J* 4.5), 5.20–5.25 (2H, m), 7.0–7.4 (10H, m); MS *m*/*z* 501 (M^+). Anal. Calcd for $C_{29}H_{31}N_3O_5$: C, 69.44; H, 6.23; N, 8.38. Found: C, 69.43; H, 6.26; N, 8.44.

4.4.3. Compound 17. 0.31 g, 51%. Pale yellow powder; mp 83 °C (from diisopropyl ether); $[\alpha]_D^{25} = -56.6$ (*c* 0.37, $CHCl_3$); IR (Nujol) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (3H, s), 1.31 (3H, s), 1.80–2.50 (6H, m), 3.14 (1H, dd, *J* 12.2, 5.2), 3.31 (1H, dd, *J* 12.2, 9.0), 3.85 (3H, s), 3.90 (1H, d, *J* 12.5), 4.24 (1H, dd, *J* 11.3, 4.5), 4.43 (1H, d, *J* 12.5), 5.07 (1H, dd, *J* 9.0, 5.2), 7.2–7.4 (10H, m); MS *m*/*z* 501 (M^+). Anal. Calcd for $C_{29}H_{31}N_3O_5$: C, 69.44; H, 6.23; N, 8.38. Found: C, 69.47; H, 6.26; N, 8.44.

4.4.4. Compound 18. 0.22 g, 37%. Pale yellow powder; mp 114 °C (from diisopropyl ether); $[\alpha]_D^{25} = +23.3$ (*c* 0.28, $CHCl_3$); IR (Nujol) 1740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (3H, s), 1.18 (3H, s), 1.80–2.50 (6H, m), 3.20 (1H, dd, *J* 12.2, 5.3), 3.35 (1H, dd, *J* 12.2, 9.0), 3.86 (3H, s), 3.90 (1H, d, *J* 12.4), 4.20 (1H, dd, *J* 11.3, 4.5), 4.40 (1H, d, *J* 12.4), 5.11 (1H, dd, *J* 9.0, 5.3), 7.0–7.4 (10H, m); MS *m*/*z* 501 (M^+). Anal. Calcd for $C_{29}H_{31}N_3O_5$: C, 69.44; H, 6.23; N, 8.38. Found: C, 69.47; H, 6.26; N, 8.44.

4.5. Hydrolysis of major cycloadducts 11, 13, 15 and 17

A solution of the appropriate major cycloadduct **11**, **13**, **15** or **17** (0.5 mmol) in tetrahydrofuran (6 mL) and 2 M aqueous sodium hydroxide (6 mL) was stirred at room temperature for 4 h. The mixture was then extracted with ethyl acetate (2 × 25 mL). The organic layer was washed with water (25 mL), dried over sodium sulfate and evaporated to give the starting chiral auxiliary: compound **5** was recovered from **11** (0.13 g, 80%) and **15** (0.14 g, 85%); compound **6** was recovered from **13** (0.14 g, 83%) and **17** (0.14 g, 85%).

Aqueous hydrochloric acid (1 M) was added to the mother liquor to pH 3, and the mixture extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with water (25 mL), dried over sodium sulfate and evaporated.

Crystallization from chloroform–ethanol gave pure (*S*)-(+)-**19**. From **11**: 106 mg, 86%; $[\alpha]_D^{25} = +5.7$ (*c* 0.40, DMSO); from **13**: 110 mg, 90%; $[\alpha]_D^{25} = +5.6$ (*c* 0.40, DMSO) {lit. $[\alpha]_D^{25} = +5.5$ (*c* 0.40, DMSO)}.

Crystallization from chloroform–ethanol gave pure (*S*)-(+)-**20**. From **15**: 85 mg, 89%; $[\alpha]_D^{25} = +62.0$ (*c* 0.94, $CHCl_3$); from **17**: 88 mg, 92%; $[\alpha]_D^{25} = +62.2$ (*c* 1.00, $CHCl_3$) {lit. $[\alpha]_D^{25} = +64.0$ (*c* 1.04, $CHCl_3$)}.

Acknowledgements

Thanks are due to MURST and CNR for financial support. We thank the NMR technician Dr. Lara De Benassuti, University of Milan, for NOE experiments.

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