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TETRAHEDRON: *ASYMMETRY*

The first example of a (1*R*,2*S*,5*R*)-(−)-menthyl chiral auxiliary in intramolecular nitrilimine cycloadditions: synthesis of enantiopure pyrazolo[1,5-*a*][4,1]benzoxazepines and pyrazolo[1,5-*a*][4,1]benzodiazepines

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Abstract

By using (1*R*,2*S*,5*R*)-(−)-menthyl as a chiral auxiliary, we have developed a synthesis of hydrazonoyl chlorides **2** and **8**, treatment of which with silver carbonate promoted the in situ generation of the corresponding nitrilimines **3** and **9**. The latter underwent intramolecular cycloaddition giving, respectively, enantiopure pyrazolo[1,5-*a*][4,1]benzoxazepines **4**, **5** and pyrazolo[1,5-*a*][4,1]benzodiazepines **10**. © 1999 Elsevier Science Ltd. All rights reserved.

Stereoselective cycloadditions of nitrilimines have been recently exploited in order to obtain enantiomerically pure pyrazole derivatives. Chiral dipolarophiles,[1–3] as well as homochiral nitrilimines,[4] were employed for this purpose. There is, however, a dearth of the intramolecular version of this methodology in the literature, the only reports available being two recent papers from our laboratory.[5,6] We have now examined in more detail the behaviour towards stereoselection of various kinds of nitrilimines in which the chiral unit is placed inside the tether joining the reactive groups. In pursuing our interest in this field, and recognizing the growing attention towards chiral auxiliaries in cycloadditions,[7,8] we present here the first example in which the chiral auxiliary, namely the (1*R*,2*S*,5*R*)-(−)-menthyl group, is placed outside the tether joining the reactive groups.

Firstly, we devised (1*R*,2*S*,5*R*)-(−)-menthyl-2-chloroacetoacetate[4] as a readily accessible chiral building block for the synthesis of both hydrazonoyl chlorides **2** and **8** (see Schemes 1 and 2).[9] Since compound **2** was prepared starting from racemic **1**,[10] it was obviously obtained as an equal mixture of diastereoisomers, which was unfortunately inseparable by standard chromatographic methods. On the other hand, hydrazonoyl chloride **8** was synthesised in enantiopure form. Nitrilimine intermediates **3**

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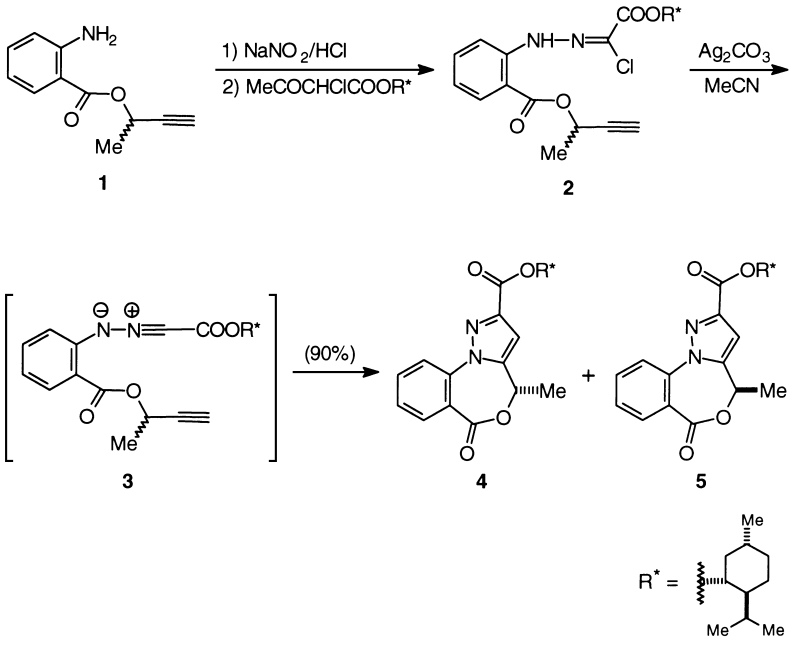
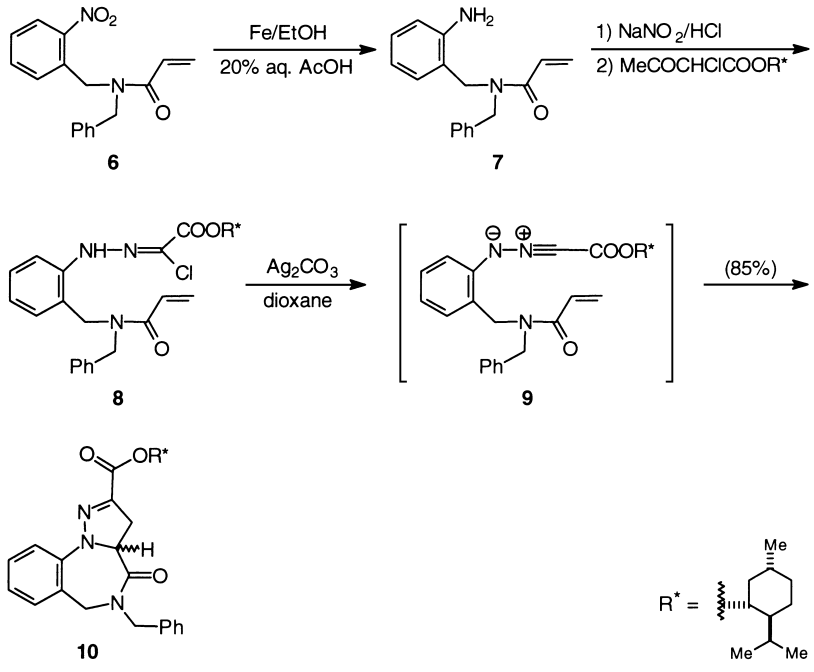
and **9** were generated in situ by treating a 0.02 M solution of the corresponding hydrazonoyl chlorides in dry acetonitrile (or dioxane, respectively) with silver carbonate at room temperature, following a well-established procedure described by our group.[11] The extent of intramolecular cycloadditions was fully satisfactory, since the diastereoisomeric pyrazolo[1,5-*a*][4,1]benzoxazepines **4**, **5** and pyrazolo[1,5-*a*][4,1]benzodiazepines **10** were obtained with 90 and 85% yields, respectively. The separation of cycloadducts **4**, **5** and **10** in their enantiopure form was achieved by simple crystallisation from diisopropyl ether–methanol.[12] Furthermore, the slow evaporation of a solution of **5** in methanol gave crystals in a suitable form for X-ray crystallographic analysis.[13] The absolute configuration of the stereocentre generated in the oxazepinic ring of **5** was (*R*) (see Fig. 1). Attempts to obtain a single crystal from either of the diastereoisomers **10** failed, since they were obtained as amorphous solids; the absolute configuration of the newly-formed stereocentre remains undetermined.



Scheme 1.

In the case of nitrilimine **3**, no new stereocentres originate from the intramolecular cycloaddition, and the (1*R*,2*S*,5*R*)-(−)-menthyl group just allows the separation of enantiopure cycloadducts **4** and **5** from the diastereoisomeric mixture. This target is a relevant one, in that (i) enantiopure pyrazolo[1,5-*a*][4,1]benzoxazepines are still largely absent in the literature, and (ii) our synthetic route starts from racemic **1**, which is easily prepared, thus avoiding the tedious synthesis of enantiomerically pure 3-butyn-2-ol.

The (1*R*,2*S*,5*R*)-(−)-menthyl group could act as a genuine chiral auxiliary in the intramolecular cycloaddition of nitrilimine **9**. As far as stereoselection is concerned, ^{1}H NMR analysis of the reaction crude revealed that cycloadducts **10** were an equimolecular mixture of diastereoisomers. This lack of diastereopreference may be due to the distance between the chiral auxiliary and the reactive groups. Although the good intramolecular cycloaddition yields make the nitrilimine protocol a suitable tool in the construction of the enantiopure pyrazolo[1,5-*a*][4,1]benzodiazepine system, the inefficiency of the (1*R*,2*S*,5*R*)-(−)-menthyl group as the chiral auxiliary in this type of cycloaddition must be acknowledged.



Scheme 2.

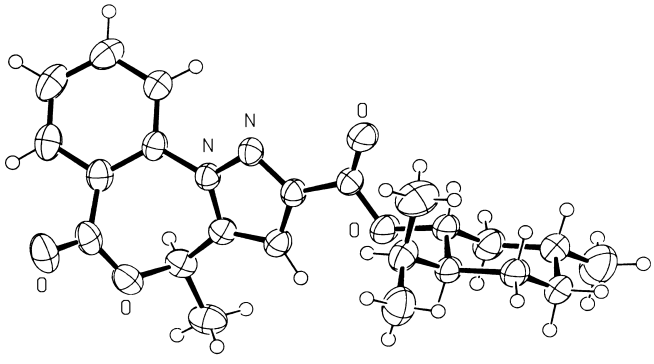


Figure 1. Ortep plot of **5**. Ellipsoids are at 50% of probability level

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9. Selected data for compounds **6**, **7**, **2** and **8**. Compound **6**: (68% yield) m.p. 126°C (from diisopropyl ether); IR: (Nujol) 1650 cm^{-1}; ^1H NMR δ: ($CDCl_3$) 4.63 (2H, s), 4.96 (2H, s), 5.75 (1H, dd, *J* 19.6, 9.7), 6.50 (1H, dd, *J* 19.6, 2.2), 6.67 (1H, dd, *J* 9.7, 2.2), 7.05–8.10 (9H, m); MS: *m/z* 296 (M^+). Compound **7**: (70% yield) m.p. 102°C (from diisopropyl ether); IR: (Nujol) 3410, 3350, 3230, 1635 (cm^{-1}); ^1H NMR δ: ($CDCl_3$) 4.50 (2H, s), 4.58 (2H, s), 4.70 (2H, br s), 5.75 (1H, dd, *J* 9.3, 4.3), 6.50–6.70 (2H, m), 6.85–7.40 (9H, m); MS: *m/z* 266 (M^+). Compound **2**: (70% yield) gum; IR: (Neat) 3240, 1720, 1690 (cm^{-1}); ^1H NMR δ: ($CDCl_3$) 0.80 (3H, d, *J* 6.9), 0.93 (6H, d, *J* 7.1), 1.65 (3H, d, *J* 6.7), 1.20–2.20 (9H, m), 2.51 (1H, d, *J* 2.2), 4.83 (1H, ddd, *J* 10.9, 10.7, 4.4), 5.72 (1H, dq, *J* 6.7, 2.2), 6.90–8.05 (4H, m), 11.60 (1H, br s); MS: *m/z* 432 (M^+). Compound **8**: (65% yield) m.p. 49°C (from diisopropyl ether); $[\alpha]_D^{25}$=−57.6 (MeOH, c=0.072); IR: (Nujol) 3170, 1725, 1645 (cm^{-1}); ^1H NMR δ: ($CDCl_3$) 0.84 (3H, d, *J* 7.0), 0.95 (6H, d, *J* 6.7), 1.10–2.10 (9H, m), 4.57 (2H, s), 4.63 (1H, d, *J* 14.8), 4.70 (1H, d, *J* 14.8), 4.86 (1H, ddd, *J* 10.9, 10.7, 4.4), 5.78 (1H, dd, *J* 8.0, 4.3), 6.50–6.60 (2H, m), 6.93–7.69 (9H, m), 10.50 (1H, br s); MS: *m/z* 509 (M^+).
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12. Selected data for compounds **4**, **5** and **10**. Compound **4**: (45% yield) m.p. 70°C (from diisopropyl ether–methanol); $[\alpha]_D^{25}$=−29.0 (MeOH, c=0.20); IR: (Nujol) 1740, 1700 (cm^{-1}); ^1H NMR δ: ($CDCl_3$) 0.80 (3H, d, *J* 7.0), 0.90 (3H, d, *J* 7.2), 0.93 (3H, d, *J* 7.2), 1.85 (3H, d, *J* 6.8), 1.10–2.10 (9H, m), 4.94 (1H, ddd, *J* 10.8, 10.5, 4.4), 5.28 (1H, q, *J* 6.8), 6.92 (1H, s), 7.42–8.00 (4H, m); MS: *m/z* 396 (M^+). Compound **5**: (45% yield) m.p. 162°C (from diisopropyl ether–methanol); $[\alpha]_D^{25}$=−155.0 (MeOH, c=0.08); IR: (Nujol) 1740, 1700 (cm^{-1}); ^1H NMR δ: ($CDCl_3$) 0.82 (3H, d, *J* 7.0), 0.94 (6H, d, *J* 7.3), 1.85 (3H, d, *J* 6.8), 1.10–2.10 (9H, m), 5.00 (1H, ddd, *J* 11.0, 10.8, 4.4), 5.25 (1H, q, *J* 6.8), 6.94 (1H, s), 7.36–8.05 (4H, m); MS: *m/z* 396 (M^+). Compound **10** (first diastereoisomer): (42% yield) m.p. 123°C (from diisopropyl ether–methanol); $[\alpha]_D^{25}$=+112 (MeOH, c=0.36); IR: (Nujol) 1720, 1670 (cm^{-1}); ^1H NMR δ: ($CDCl_3$) 0.84 (3H, d, *J* 6.9), 0.95 (6H, d, *J* 6.6), 1.10–2.18 (9H, m), 3.29 (1H, dd, *J* 17.9, 13.5), 3.83 (1H, d, *J* 16.8), 4.14 (1H, dd, *J* 17.9, 9.0), 4.50 (1H, d, *J* 14.8), 4.90 (1H, ddd, *J* 10.7, 10.5, 4.3), 4.97 (1H, d, *J* 14.8), 5.31 (1H, d, *J* 16.8), 5.74 (1H, dd, *J* 13.5, 9.0), 6.76–8.25 (9H, m); MS: *m/z* 473 (M^+). Compound **10** (second diastereoisomer): (42% yield) m.p. 90°C (from diisopropyl ether–methanol); $[\alpha]_D^{25}$=−96.8 (MeOH, c=0.28); IR: (Nujol) 1720, 1665 (cm^{-1}); ^1H NMR δ: ($CDCl_3$) 0.80 (3H, d, *J* 6.8), 0.88 (6H, d, *J* 6.5), 1.10–2.10 (9H, m), 3.22 (1H, dd, *J* 18.1, 13.6), 3.79 (1H, d, *J* 16.8), 4.13 (1H, dd, *J* 18.1, 8.9), 4.43 (1H, d, *J* 14.8), 4.84 (1H, ddd, *J* 10.8, 10.7, 4.4), 4.97 (1H, d, *J* 14.8), 5.27 (1H, d, *J* 16.8), 5.72 (1H, dd, *J* 13.6, 8.9), 6.72–7.68 (9H, m); MS: *m/z* 473 (M^+).
13. Crystal data for compound **5**. $C_{23}H_{28}N_2O_4$, Fw=396.47, monoclinic, space group $P2_1$, *a*=7.7599(5), *b*=11.4865(10), *c*=11.8772(7) Å, β=96.100(5)°, *V*=1052.7(2) $Å^3$, *Z*=2, D_x=1.251 Mg m^{-3}, μ (Mo-Kα)=0.086 mm^{-1}; crystal dimensions 0.56×0.34×0.32 mm^3, λ=0.71073 Å (Mo-Kα radiation, graphite monochromator, Siemens P4 diffractometer). Data collection at 291 K, ω–2θ scan mode, 4<2θ<55°, *h* 0→10, *k* −14→14, *l* −15→15; 5177 collected reflections, 2538 unique [2299 with $I_o>2\cdot\sigma(I_o)$], merging *R*=0.0174. The structure was solved by SIR92 [Altomare, A.; Cascarano, G.; Giacovazzo, G.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, G. *J. Appl. Cryst.* **1994**, *27*, 435] and refined by SHELXL-97 [Sheldrick, G. M. (1997). *SHELXL-97. Program for the Refinement of Crystal Structures*; University of Göttingen: Germany] by full-matrix least-squares based on F_o^2, with weights $w=1/[\sigma^2(F_o)^2+(0.0432P)^2+0.0112P]$, where $P=(F_o^2+2F_c^2)/3$. The final consistency indices were *R*=0.0314 and *Rw*=0.0721 (0.0276 and 0.0701, respectively, for observed reflections), goodness-of-fit=1.027. The final map ranges between −0.11 and 0.13 e/$Å^3$. The absolute configuration was determined on the base of the known one of menthyl moiety.