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# Enantiospecific Synthesis of Substituted Bicyclo[2.1.1]hexane-1-carboxylic Acids and Esters

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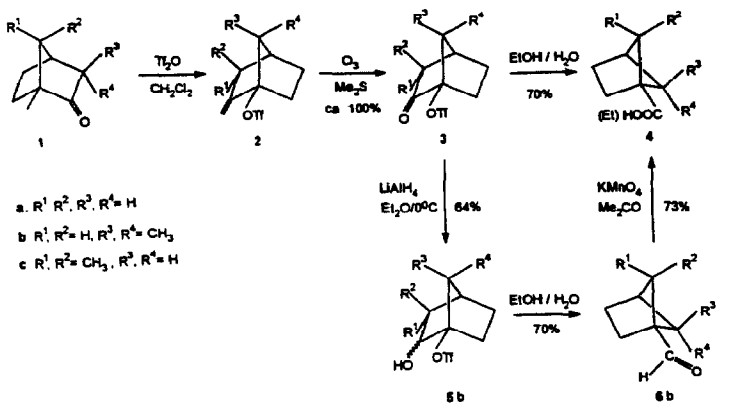
**Abstract:** *The base promoted ring contraction of the readily accessible homochiral 2-oxo-1-norbornyl triflates 3 in 60% ethanol takes place with formation of bicyclo[2.1.1]hexane (4a), (+)- or (-)-7,7-dimethyl-bicyclo[2.1.1]hexan-1-carboxylic acids (4c or 4b) and the corresponding ethyl esters in good yields.*

Bridgehead substituted bicyclo[2.1.1]hexanes are of particular interest because of the noticeable effects of bond angle deformation on their reactivity[1,2]. The most convenient precursors for this type of compounds are the corresponding carboxylic acids **4**, which are readily converted to other functional groups, e.g. halogen, amine and hydroxyl[3]. However, until now the only available routes for the synthesis of the acids **4** are very complicated. Thus, the acid **4a** was first obtained by a twelve-steps synthesis from norbornane[4]. Modern synthesis of **4a**[3] and **4b** + **4c** [(±)-**4b**] are six-step processes from the Diels-Alder adduct of cyclopentadiene and acrylic or 3,3-dimethylacrylic acid[3,5]. The last step of these synthesis is the base-promoted ring contraction of (±)-1-bromo-2-norbornanone or (±)-1-bromo-7,7-dimethyl-2-norbornanone which give high yield of the acid **4c** but very low yield (ca. 4%) of the acid (±)-**4b** under similar conditions[3,5].

In continuation of our work on the enantiospecific synthesis of homochiral intermediates from naturally occurring 2-norbornanones, we report here on the base-promoted ring contraction of 2-oxo-1-norbornyl triflates **3**[6] ($EtOH/H_2O$ 60:40, $Et_3N$, 130°C, 120h) to afford a mixture of products **4**, as a mixture of the acid and the ester in 51:36 ratio in high overall yield (**4a**: 86%, **4b**: 20%, **4c**: 80%). Higher yields of **4b** can be obtained from the solvolysis of the alcohol **5b**, prepared by reduction of **3b**. This avoids the steric hindrance in the solvolysis[3] of **3b**, using as substrate the alcohol **5b**, prepared by reduction of **3b**. The acid **4b** is now obtained by oxidation of the solvolysis product, the aldehyde **6b**[7]. Use of strong base for the solvolysis reaction such as sodium hydroxide[3,5] leads to O-S scission. On the other hand, in the poorly nucleophilic solvent hexafluoroisopropanol, no solvolysis products were detected after two weeks at 140°C.




The pure acids **4**[8] were isolated from the reaction mixture by extraction with NaOH and acidification and the pure esters **4**[9] by column chromatography on silica gel (pentane/ether = 95:5). The acids can be converted into the esters or vice versa, increasing the yield of the total product to more than 80%. The $[\alpha]_D$ absolute values for **4b** and **4c** are the same, although these compounds were prepared from different starting materials and agree with those reported in the literature[7]. This facts vouch for the enantiospecificity of our method.

The triflates **3**[6] are obtained by ozonolysis of the corresponding 2-methyliden-1-norbornyl triflates **2** in quantitative yield. The triflates **2**[10] are synthesized by reaction of (±)-1-methyl-2-norbornanone (**1a**)(60 %), (+)-camphor (95 %) or (-)-fenchone (78 %) with triflic anhydride and *N,N*-diisobutyl-2,4-dimethyl-3-pentylamine in $CH_2Cl_2$ at room temperature[11].

In conclusion, our procedure utilizing triflate as the leaving group instead of the bromide[3,5], is a very useful approach to the synthesis of bicyclo[2.1.1]hexanes and, together with the solvolysis of 2,3,3-trimethyl-1-norbornyl triflate[12] which takes place also with ring contraction, constitutes the first asymmetric synthesis of optically active bicyclo[2.1.1]hexanes.

## References and Notes

1) Wu, Y. D.; Kirmse, W.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4557. 2) Della, E. W.; Head, N. J. *J. Org. Chem.* **1992**, *57*, 2850. 3) Abeywickrema, R. S.; Della, E. W. *Org. Prep. Proc. Int.* **1980**, *12*, 357. 4) Wiberg, K. B.; Lowry, B. R. *J. Am. Chem. Soc.* **1963**, *85*, 3188. 5) Fong, W. C.; Thomas, R.; Scherer, K. V. *Tetrahedron Lett.* **1971**, 3789. 6) **3b**: $[\alpha]_D^{20}$= +21.0 (c= 1.0; MeOH); **3c**: $[\alpha]_D^{20}$= -12.3 (c=2.1; MeOH) 7) Ebisu, K.; Batty, L. B.; Higaki, J. M.; Larson, H. D. *J. Am. Chem. Soc.* **1965**, *87*, 1399. 8) **4a**($CO_2H$): s. lit.[4] $^{13}$C-NMR($CDCl_3$): δ = 180.64, 51.69, 41.66, 36.53, 28.93, 27.37; **4b**($CO_2H$): s. lit.[7] $^{13}$C-NMR($CDCl_3$): δ= 180.62, 55.29, 49.37, 43.84, 37.95, 29.29, 25.82, 19.49, 19.41. $[\alpha]_D^{20}$= +1.4 (c= 1.1; MeOH); -10.4 (c= 4.95; benzene) 9) **4a**($CO_2Et$): $^{13}$C-NMR($CDCl_3$): δ= 174.00, 59.97, 53.00, 41.72, 36.44, 29.05, 27.47, 14.17. **4b**($CO_2Et$): $^{13}$C-NMR($CDCl_3$): δ= 173.75, 59.70, 55.50, 48.97, 43.65, 38.00, 29.16, 25.89, 19.60, 19.48, 14.46. $[\alpha]_D^{20}$= -2.3 (c=1.9; MeOH) 10) **2b**: $[\alpha]_D^{20}$= +16.5 (c= 5.3; MeOH) **2c**: s. lit.[11] 11) Martínez, A. G.; Teso, E.; Osío, J.; Manrique, J.; Rodriguez, E.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1992**, *33*, 607. 12) Martínez, A. G.; Teso E.; García, A.; Osío, J.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1989**, *30*, 1503.