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SYNTHESIS OF OPTICALLY ACTIVE 3-OXA-CARBACYCLIN PRECURSORS FEATURING ASYMMETRIC HORNER-EMMONS REACTION

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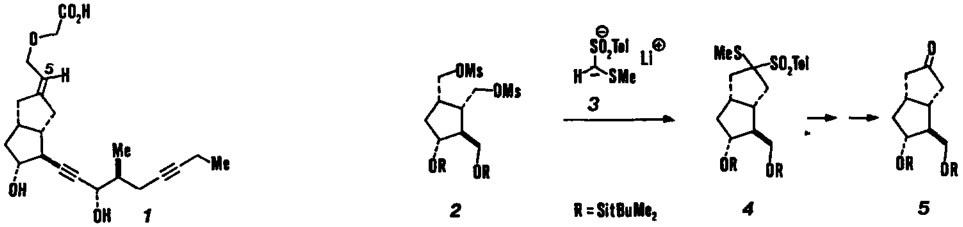
Summary: An enantioselective synthesis of 5 is described. Asymmetric Horner-Emmons reactions with the chiral phosphonate 6 are key steps in the synthesis of the allylic alcohols *E*-8 and *E*-11 from the ketones 5 and 9, respectively.

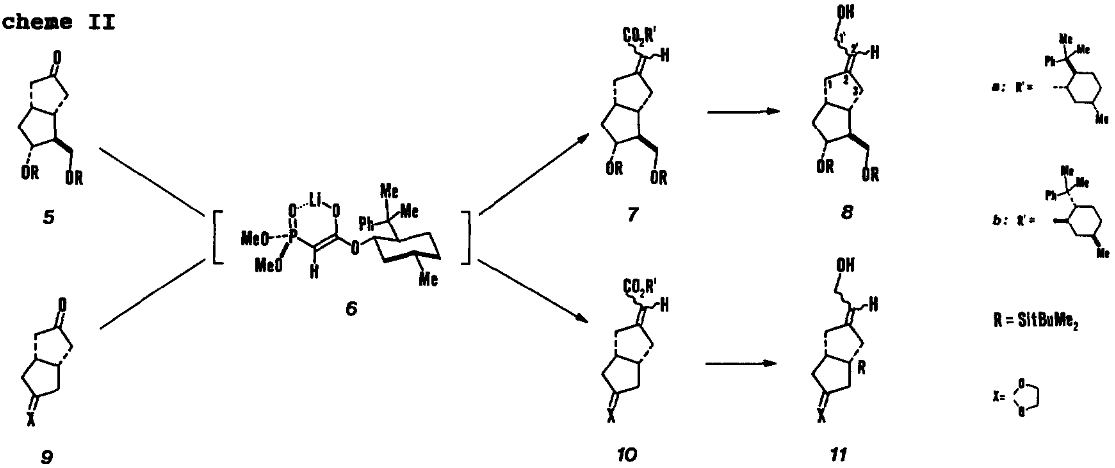
The 5*E*-3-oxa-carbacyclin 1,[1a] a stable and orally active mimic of the unstable prostacyclin, shows promise for the treatment of peripheral arterial occlusive disease.[1b] A key intermediate in the synthesis of 1 as well as of other carbacyclins[2] is the bicyclic ketone 5.[3] Introduction of the C1-C5 segment of 1 via olefination of 5 with *achiral* phosphonoacetates, however, proved to be *unselective* due to the *small inherent bias* of 5 towards *E*-selectivity[1a,c] leading finally to a 1:1-mixture of 1 and its biologically much less active 5*Z*-isomer. We report herein on a new synthesis of optically active 5 and its selective conversion to the allylic alcohol *E*-8, the precursor for 1, by using a reagent controlled olefination with the *chiral* lithio phosphonate 6 as key step.[4,5]

Scheme I.



Cycloalkylation of the lithium sulfone 3[6] (5 equiv, THF, HMPT, -78 °C to 10 °C) with optically active dimesylate 2[2c] yielded a mixture of the epimeric bicyclic sulfones 4 (85%) which gave upon hydrolysis (50% H_2SO_4/ethanol, 1:25, 70 °C) and subsequent reprotection (*t*BuMe$_2$SiCl, DMF, ImH) of the corresponding keto-diol the ketone 5 {$[\alpha]_D^{20}$ -28.5° (*c* 0.55, acetone)} in overall 75% yield based on 2 (Scheme I). The routes leading to 2 and 5 are amendable to large-scale. Olefination of 5 (THF, 0.17 M) with the lithio phosphonoacetate 6[7] (3 equiv, THF, 0.50 M, -60 °C, 7 d) led to a mixture of the isomeric esters *E*-7a and *Z*-7a in 95% combined yield and a ratio of 86:14 (Scheme II). By using *ent*-6 (3 equiv, THF, -60 °C, 7 d) the sense of asymmetric induction was reversed to give *E*-7b and *Z*-7b in 89% yield however in a ratio of 23:77. Interestingly, when 5 was treated with *ent*-6 at 46 °C instead of -60 °C the sense of asymmetric induction was the same as with 6 giving a mixture of *E*-7b and *Z*-7b in a ratio of 67:33 and 90% yield.

Scheme II



Reduction of *E/Z*-7a with diisobutylaluminium hydride (DIBAH)(2.5 equiv, THF, 0 °C) and subsequent diastereomer separation by MPLC furnished in 77% yield the allylic alcohol *E*-8 {$[\alpha]_D^{20}$ -6.1° (*c* 0.97, CH_2Cl_2)} besides *Z*-8 (12%) and (+)-8-phenylmenthol (96%). The configuration of *Z*-8 and thus also of *E*-8 was unequivocally ascertained by 400-MHz ^1H NMR spectroscopy using decoupling and COSY experiments for the assignment of each proton in the NMR spectrum and NOE experiments for the establishment of a *syn* relationship between 1-H and 2'-H as well as between 3-H and 1'-H.

Asymmetric Horner-Emmons reaction[5] of the *achiral* ketone 9 (THF, 0.16 M) with 6 (1.7 equiv, THF, 0.27 M, -60 °C, 4 d) cleanly afforded in 93% yield a mixture of the diastereomeric esters *E*-10a and *Z*-10a in a ratio of 95:5. At higher temperatures selectivity as well as reaction time decreases (at 25 °C; 71:29, 2.5 h). Reduction of *E/Z*-10a (90% *de*) with DIBAH gave the chiral allylic alcohol *E*-11 of 90% *ee* {$[\alpha]_D^{25}$ +17.5° (*c* 1.38, CH_2Cl_2)} in 90% yield. Compound *E*-11 should be an attractive precursor for the synthesis of 1.

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References and Notes

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2. For recent syntheses of carbacyclins, see: (a) P. Magnus, D. P. Becher, *J. Am. Chem. Soc.* 1987, *109*, 7495. (b) Y. Nagao, T. Nakamura, M. Ochiai, K. Fuji, E. Fujita, J. Chem. Soc. Chem., Commun. 1987, 267. (c) H.-J. Gais, W. A. Ball, J. Bund, *Tetrahedron Lett.*, in press.

3. B. Bennua, H. Dahl, H. Vorbrüggen, *Synthesis* 1986, 41 and references therein.

4. H. Rehwinkel has independently developed similar methodology: H. Rehwinkel, J. Skupsch, H. Vorbrüggen, following communication in this issue. We are indebted to him for sharing his unpublished results prior to publication.

5. For asymmetric Wittig-type reactions, see: S. Hanessian, D. Delorme, S. Beaudoin, Y. Leblanc, *J. Am. Chem. Soc.* 1984, *106*, 5754 and references therein.

6. K. Ogura, N. Yahata, I. Watanabe, K. Takahashi, H. Iida, *Bull. Chem. Soc. Jpn.* 1983, *56*, 3543.

7. The lithium salt 6 {100-MHz ^1H NMR ([D_8]THF) δ 2.50 (d, *J* = 14 Hz, 1H), 3.50 (d, *J* = 11 Hz, 3H), 3.51 (dd, *J* = 11 Hz, 3H), 4.70 (sm, 1H)} was prepared conveniently from (+)-8-phenylmenthol (Merck-Schuchardt) by esterification with dimethylphosphonoacetic acid (DCC, DMAP, CH_2Cl_2, 25 °C) to the corresponding phosphonoacetate {$bp_{0.01}$ 120 °C, $[\alpha]_D^{20}$ +17.7° (*c* 2.23, CH_2Cl_2)} in 92% yield (cmp.: S. Hatekeyama, K. Satoh, K. Sakurai, S. Takano, *Tetrahedron Lett.* 1987, *28*, 2713) followed by lithiation with *n*-BuLi (THF, -78 °C to 0 °C).

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