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CYCLOBUTANONES FOR THE STEREOSELECTIVE SYNTHESIS OF BIFUNCTIONAL MACROLIDE INTERMEDIATES[1]

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Abstract. - Beckmann fragmentation of the oximes 5 and 6 respectively, which were derived from the cyclobutanones 3 and 4, furnished the bifunctional five carbon units 7 and 8 with ca. 98% and 91% stereoselectivity.

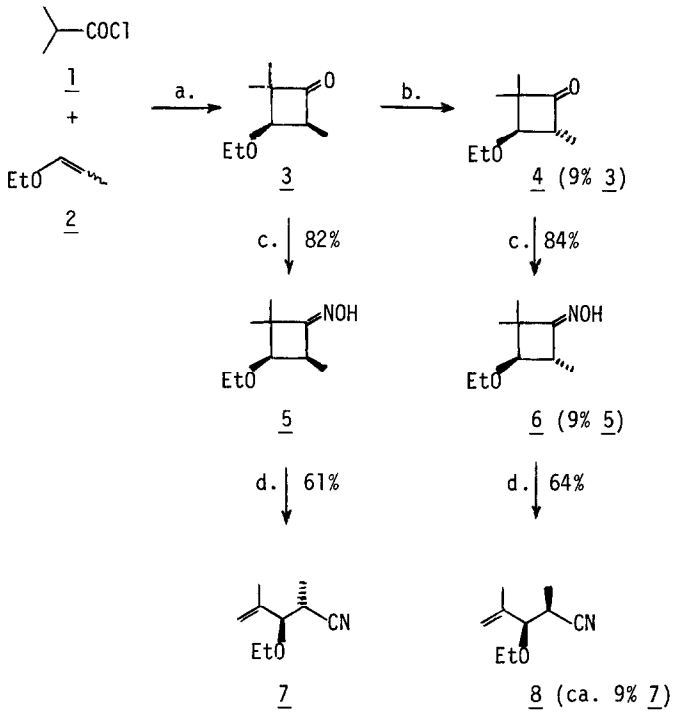
We were interested for some time in the possible control of vicinal stereochemistry in open chain compounds[2]. A most successful approach to this task turned out to be the controlled aldol-reaction[3].

The more classical way to meet this problem is to stereoselectively construct a cyclic intermediate, which subsequently can be converted into an open chain compound. In Scheme 1[4] a novel combination of reactions is shown, which leads to the diastereomeric bifunctional five carbon units 7 and 8 with 98% and 91% stereoselectivity, respectively.

Addition of dimethylketene to cis,trans-ethyl-propenylether (2)[5] furnished 3 in 90% yield (kinetic control). Equilibration (C_2H_5OH, cat. $C_2H_5O^-Na^+$) established the thermodynamic mixture, consisting of 91% 4 and 9% 3.

The corresponding oximes from 3 and 4 were prepared under standard conditions in high yield. Both were syn-anti mixtures in ∿ 60:40 ratio; bp. 72-74°C at 0.08 mm; NMR ($CDCl_3$, 400 MHz): 5 H-C(3) two doublets at 3.66 and 3.53 ppm, J(3.4) ∿ 8 Hz; 6 H-C(3) two doublets at 3.3 and 3.28 ppm, J(3.4) ∿ 6.5 Hz.[6]

Scheme 1



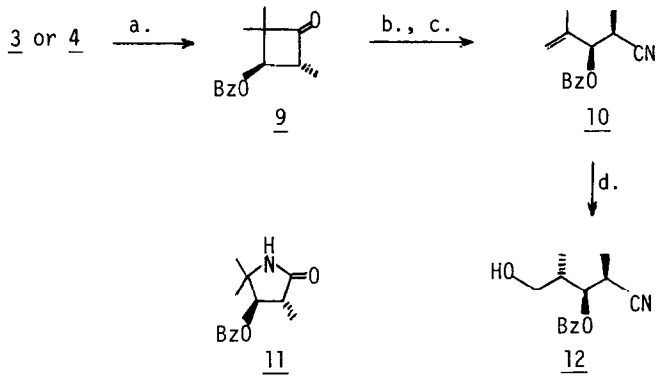
a. Et_3N, t-$BuOCH_3$: 90%, b. EtOH, cat. EtO^-Na^+, c. $NH_2OH \cdot HCl$, EtOH, H_2O, $KHCO_3$, d. m-Nitrobenzoylchloride in CH_2Cl_2, r.t.

Treatment of 5 and 6 respectively with m-nitrobenzoylchloride in CH_2Cl_2 at ambient temperature furnished 7 ind 61% and 8 in 64% yield.[7] Another condition for the Beckmann fragmentation[8] was in pyridine, t-butylmethylether and addition of $(CF_3CO)_2O$ between 20-50°C, which led to 7 and 8 in 45-50% yield.

B.p. 68-70° at 10 mm. NMR. ($CDCl_3$, 400 MHz): 7: 5.1-5.08 and 5.04-5.02 (two m; 2H-C(5), 3.64 (d; J(3.2) ~ 9 Hz; H-C(3)), 3.55-3.32 (m; O-$\underline{CH_2}$-), 2.73 (dxq; H-C(2)), 1.65 (narrow m; CH_3-C(4)), 1.22 (t; $\underline{CH_3}$-CH_2-), 1.21 (d; CH_3-C(2)); 8: 5.13-5.1 and 5.08-5.06 (two m; 2H-C(5)), 3.66 (d; J(3.2) ~ 8 Hz, H-C(3)), 3.55-3.28 (m; O-$\underline{CH_2}$-), 2.8 (dxq; H-C(2)), 1.72 (narrow m; CH_3-C(4)), 1.35 (d; CH_3-C(2)), 1.19 (t; $\underline{CH_3}$-CH_2). Both in GLC and NMR spectrum of 8 about 9% of 7 was detectable.

Thus the two bifunctional C-5 units, the R*,S*-product 7 (> 98% stereoselectivity) and the R*,R*-product 8 (> 90% stereoselectivity) have been synthetized.[9]

Scheme 2

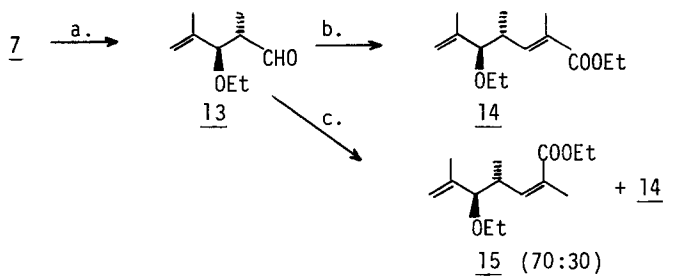


a. Benzylalcohol, cat. NaH, 80%, b. $NH_2OH \cdot HCl$, EtOH, H_2O, $KHCO_3$: 80%, c. $SOCl_2$, ether: 65%, d. BBN, THF: 73%.

As shown in Scheme 2, 3 and 4 can be conveniently converted into the benzyloxy cycobutanone 9 by treating the ethoxy compound in tenfold excess of benzylalcohol with catalytic amounts of NaH at 35-40°C for 2 hours. The reaction intermediate in this reaction is 2,4,4-trimethylcyclobutenone[10], which we also isolated under other conditions. 9 was converted into 10 through the oxime with thionylchloride in ether at 0-5°C. Under the aforementioned conditions of the Beckmann fragmentation (pyridine, $(CF_3CO)_2O$) 10% of the Beckmann rearrangement product 11 could be isolated[11]: m.p. 105-108°C (ether-pentane), NMR: H-C(4) at 3.53 ppm, d, J(3.2) ∿ 9 Hz. Hydroboration of 10 (2 eq. BBN, THF, then 10% NaOH, H_2O_2) furnished 12 with a 9:1 stereoselectivity concerning the newly formed asymmetric carbon C(4) in 73% yield.[12,13]

On the other hand DIBAL reduction of 7[14] (Scheme 3) led to the aldehyde 13 (80%), which was further converted[15] to 14 and 15.

Scheme 3



a. DIBAL, hexane, -70°C: 80%, b. $(Ø)_3P=C(CH_3)COOC_2H_5$, DMSO, 100°: 70%, c. $(EtO)_2P(O)CH(CH_3)COOC_2H_5$, THF, NaH, -70°C → 0°C: 75%.

References and Notes

[1] Communicated at the Swiss Chemical Society in Bern, October 1982.

[2] G. Fráter, Helv. 62, 2825, 2829 (1979). - G. Fráter, Tetrahedron in print.

[3] D.A. Evans, J.V. Nelson & T.R. Traber, Topics of Stereochem. 13 (1982).

[4] All compounds had correct elemental analyses and displayed NMR and IR spectra which were in agreement with the proposed structures.

[5] R. Huisgen, L.E, Feiler & G. Binsch, Chem. Ber. 102, 3460 (1969).

[6] All oxime isomers have been separated as benzoates: syn-5-benzoate, m.p. 37-38°C; anti-5-benzoate, oil; syn-6-benzoate, m.p. 70-71°C; anti-6-benzoate, m.p. 59-60°C.

[7] The expected Beckmann rearrangement product of these reactions, ethoxy-trimethylpyrrolidone, was not isolated. It is expected to be very well water soluble.

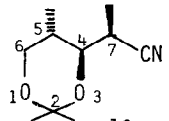
[8] " "Abnormal" Beckmann Rearrangements " R.T. Conley & S. Ghosh in "Mechanism of Molecular Migration" Ed. B.S. Thyagarajan Vol. 4, p. 197, Wiley-Interscience, 1971.

[9] See for related concepts in using ketene adducts: P. Michel, M. O'Donnell, R. Binaname, A.M. Hesbain-Frisque, L. Ghosez, J.P. Declercq, G. Germain, E. Arte & M. van Meersche, Tetrahedron Lett. 21, 2577 (1980) and literature cited therein.

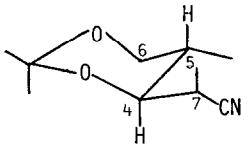
[10] H. Mayr & R. Huisgen, Angew. Chem. 87, 491 (1975), Angew. Chem., Int. Ed. Engl. 14, 499 (1975).

[11] Interestingly when the oxime derived from 9 was treated with $(\emptyset)_3P$ in CCl_4, 8 hours reflux, 11 became the main product of the reaction.

[12] The stereochemistry of the hydroboration step was determined by converting 12 into the acetonide 13 (a. H_2-Pd(C); b. acetone, PPTS).



13 ≡



NMR (400 MHz, $CDCl_3$): 3.76-3.7 (m; H_{eq}-C(6), H-C(4)), 3.55-3,49 (dxd; $J_{gem} \sim 11$ Hz; J(6.5) ~ 10 Hz; H_{ax}-C(6)), 2.88-2.81 (m; H-C(7)), 1.87-1.78 (m; H-C(5) $J(6_{ax}, 5) \sim J(4.5) \sim 10$ Hz), 1.46 and 1.41 (gem. dimethyl), 1.33 (d; CH_3-C(7)), 0.82 (d; CH_3-C(5)).

[13] For acyclic diastereoselection by hydroboration see e.g. D.A. Evans, J. Bartroli & T. Godel, Tetrahedron Lett. 23, 4577 (1982); G. Schmid, T. Fukuyama, K. Akasaka, Y. Kishi, J. Am. Chem. Soc. 101, 259 (1979).

[14] Analogous reduction of 8 (9% 7) showed ca. 20% epimerization on C(2) under our conditions.

[15] M.R. Johnson & Y. Kishi, Tetrahedron Lett. 1979, 4347.

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