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CARBAMATE MEDIATED 1,3-ASYMMETRIC INDUCTION. A STEREOSELECTIVE SYNTHESIS OF ACYCLIC 1,3-DIOL SYSTEMS

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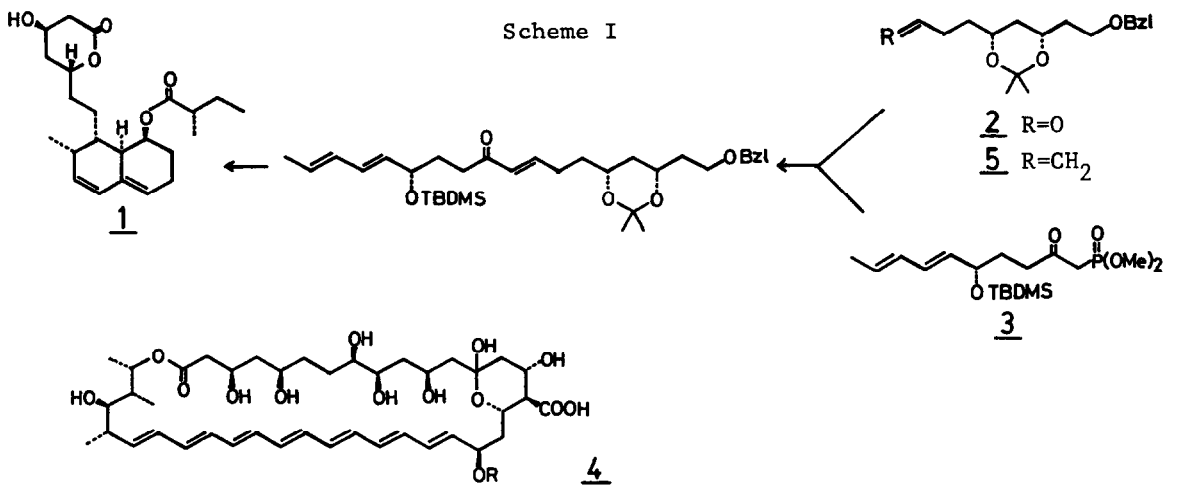
Summary: A highly regio- and stereo-selective functionalization of homoallylic carbamates with iodine is reported. The reaction has been applied to the preparation of key 1,3,5-triol intermediate 2 employed in the synthesis of compactin (1).

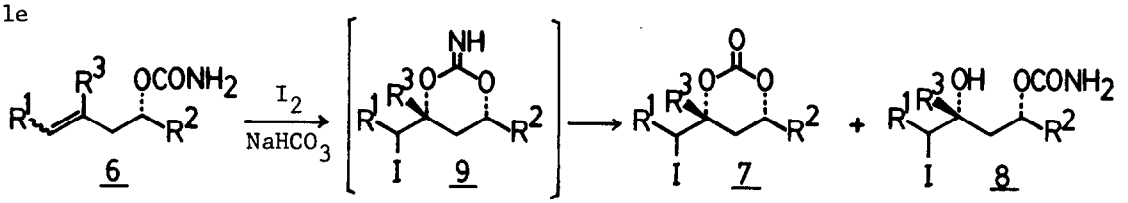
In the convergent total synthesis of compactin (ML-236B) (1),[1] the 1,3,5-triol moiety 2 was condensed with the phosphonate fragment 3 (Scheme I).[2] Similar 1,3,5-triol systems are also frequently present in polyketide-derived natural products, either as such or in masked form, e.g., as in amphotericin B (4).[3] Thus, there is considerable interest in developing general methods for the stereocontrolled synthesis of such systems.[4]

Scheme I



In the following we report a carbamate-mediated oxidative functionalization of homoallylic alcohols with efficient 1,3-asymmetric induction,[5,6] and its application in the synthesis of 2.

Table

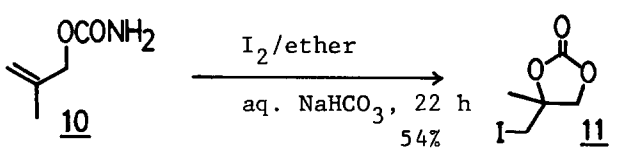


	substrate[a]	reaction time(h)	7:8[a,b]	yield(%)[b]	stereoselectivity[d]
6a	R^1=Et(Z), R^2=R^3=H	3	~100:0	68	-----
6b	R^1=CH_2OBzl(E), R^2=$(CH_2)_3OBzl$, R^3=H	39	4.4:1	76	14:1
6c	R^1=CH_2OBzl(E), R^2=$(CH_2)_2CH{=}CH_2$, R^3=H	41	4.1:1	71[c]	14:1
6d	R^1=CH_2OBzl(Z), R^2=$(CH_2)_2CH{=}CH_2$, R^3=H	42	4.6:1	96	10:1
6e	R^1=R^2=H, R^3=Me	26	~100:0	54	-----

a) See ref. 7. b) Ratios(7:8) and yields(7+8) refer to pure compounds isolated by silica gel chromatography. c) See ref. 8. d) Diastereomeric ratios were determined by 360 MHz ^{1}H-NMR after the mixtures(7+8) were transformed to the corresponding acetonides such as 5.

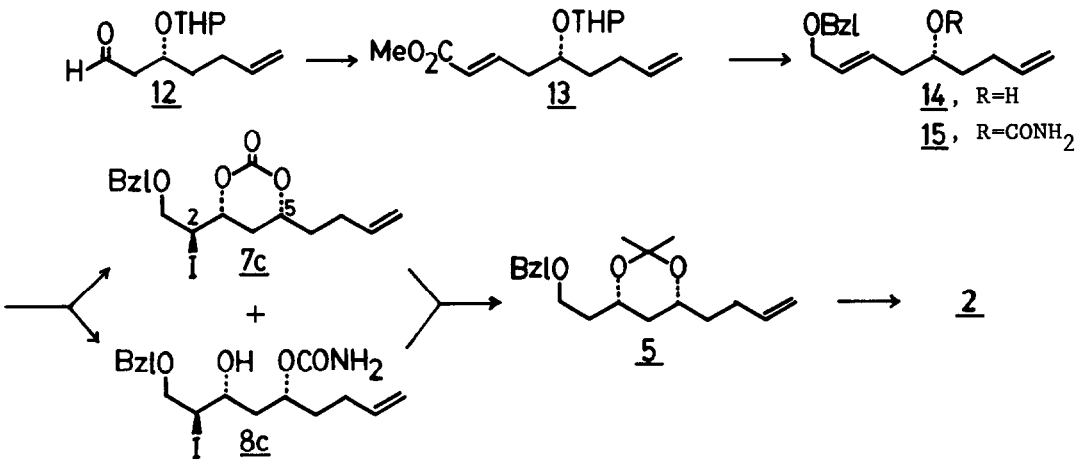
The homoallylic carbamates 6[7] were readily prepared from the corresponding alcohols in excellent yields (>90%) by brief treatment with CCl_3CONCO followed by hydrolysis (K_2CO_3-aq. MeOH/r.t./1 h).[9] Cyclofunctionalization of 6 with 2 equiv. of iodine in the two phase medium, ether/aq. satd. $NaHCO_3$ (2:1 v/v), r.t., afforded the corresponding cyclic iodocarbonates 7[7,8] and hydroxycarbamates 8[7,8] in high regio- and stereo-selectivity,[5] 54-96% yields (Table).

This cyclofunctionalization also proceeded in moderate yield in the case of allylic carbamate 10 to give five-membered carbonate 11.[7]



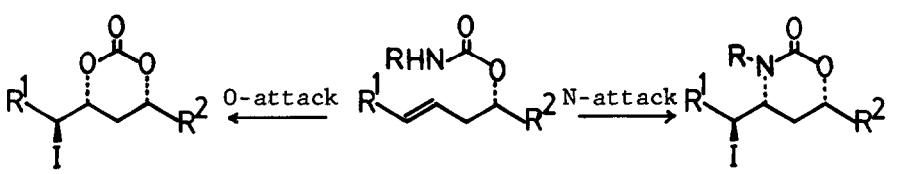
Our enantio- and stereo-selective synthesis of the 1,3,5-triol system 2 is based on a combination of the asymmetric reduction of a β-keto acid with baker's yeast[2,10] and subsequent functionalization of the homoallylic carbamate (Scheme II). The chiral THP ether 12, $[\alpha]_D^{23}$ +7.8°(c=1.0, $CHCl_3$), readily available from the corresponding β-keto ester via baker's yeast reduction,[2,10] was homologated ($Ph_3P{=}CHCOOMe/CH_2Cl_2$/r.t.) to 13,[7] 95% yield, $[\alpha]_D^{23}$ +25.8°(c=1.1, $CHCl_3$).

Scheme II



Reduction (excess DIBAH/ether/0 °C), protection ($PhCH_2Br$/NaH/DMF/r.t.) and deprotection of THP (1N-HCl/MeOH/r.t.) gave the homoallylic alcohol 14,[7] $[\alpha]_D^{23}$ -1.1°(c=1.3, $CHCl_3$), in 78% overall yield. The carbamate 15,[7] $[\alpha]_D^{23}$ +15.0° (c=1.0, $CHCl_3$), was prepared as described above, and was subjected to the iodo-functionalization to give the mixture of 7c[7,8] and 8c.[7,8] The reaction mixture, without purification, was converted to the protected 1,3,5-triol 5, $[\alpha]_D^{22}$ -16.0° (c=1.1, $CHCl_3$),[2] in 56% overall yield via three steps: (i) n-Bu_3SnH/AIBN/63 °C/1 h; (ii) 10% aq. NaOH/MeOH/63 °C/1 h; (iii) $(MeO)_2CMe_2$/CSA/CH_2Cl_2/r.t. Ozonolysis of 5 (O_3/MeOH/-78 °C, followed by Me_2S work up) gave 2, $[\alpha]_D^{22}$ -2.5° (c=1.1, $CHCl_3$), in 88% yield.[2]

Scheme III



The present method appears to be applicable to the synthesis of a number of other 1,3,5-triol systems. Furthermore, the carbamate-mediated functionalization of homoallylic alcohols should be useful for the preparation of 1,3-amino alcohol systems as well, provided the R group of the ambident nucleophilic carbamate is chosen properly so that a nucleophilic attack by nitrogen takes place (Scheme III).

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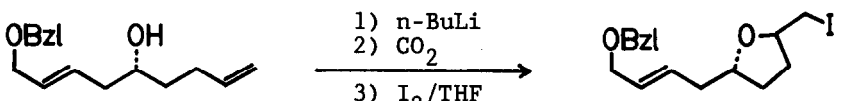
References and Notes

(1) (a) For isolation, see: A. G. Brown, T. C. Smale, T. J. King, R. Hasenkamp and R. H. Thompson, J. Chem. Soc., Perkin Trans. 1, 1165 (1976); A. Endo, M. Kuroda and Y. Tsujita, J. Antibiot., 29, 1346 (1976).
(b) For hypocholesterolemic activity, see: Y. Tsujita, M. Kuroda, K. Tanzawa, N. Kitano and A. Endo, Atherosclerosis, 32, 307 (1979); A. Yamamoto, H. Sudo and A. Endo, Ibid., 35, 259 (1980).
(2) M. Hirama and M. Uei, J. Am. Chem. Soc., 104, 4251 (1982).
(3) P. Ganis, G. Avitabile, W. Mechlinski and C. P. Schaffner, J. Am. Chem. Soc., 93, 4560 (1971); Idem, Tetrahedron Lett., 3873 (1970).
(4) A new route to chiral 1,3,5-triols using the Sharpless asymmetric epoxidation—Red-al reduction sequence has recently been reported by two groups: P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless and S. M. Viti, J. Org. Chem., 47, 1378 (1982); J. M. Finan and Y. Kishi, Tetrahedron Lett., 23, 2719 (1982) and references cited therein.
(5) A similar strategy mediated by phosphate or carbonate anion for the stereoselective functionalization of acyclic homoallylic alcohols has been reported. However, the phosphate-route [P. A. Bartlett and K. K. Jernstedt, J. Am. Chem. Soc., 99, 4829 (1979)] gave a poor yield in the case of disubstituted olefin, whereas the carbonate anion-route [G. Cardillo, M. Orena, G. Porzi and S. Sandri, J. C. S. Chem. Comm., 465 (1981)] produced tetrahydrofuran 18 almost exclusively instead of cyclic carbonate 7c from 14.[6]



14 18

(6) In a private communication, Professor P. A. Bartlett informed us that similar unfavorable cyclization occurred in the carbonate anion-mediated reaction of 4-hydroxy-1,7-diene system, and that he has discovered a more general iodofunctionalization method mediated by t-butyl carbonate.
(7) Satisfactory spectroscopic data were obtained for all new compounds described in this paper.
(8) The characteristic IR and ^{1}H NMR data of 7c and 8c were as follows: 7c, ν(film) 1762, 1252, 1217, 1192 and 1110 cm^{-1}; δ($CDCl_3$, 360 MHz) 1.75 (1H, dt, J=14 and 11.5 Hz, H-4), 2.26 (1H, dt, J=14 and 3 Hz, H-4), 4.33 (1H, ddd, J=6.7, 6.3 and 4.6 Hz, H-2), 4.43 (2H, m, H-3 and H-5). 8c, ν(film) 3450, 3350, 1710, 1095 and 1058 cm^{-1}; δ($CDCl_3$, 360 MHz) 1.85 (1H, ddd, J=14.7, 9.2 and 6.1 Hz, H-4), 2.00 (1H, ddd, J=14.7, 5.8 and 3.4 Hz, H-4), 3.78 (1H, m, H-3), 4.34 (1H, dt, J=7.4 and 5.3 Hz, H-2), 4.90 (1H, br. quintet, J=6.5 Hz, H-5).
(9) N. Minami, S. S. Ko and Y. Kishi, J. Am. Chem. Soc., 104, 1109 (1982).
(10) Details of the studies on asymmetric reductions of β-keto acid derivatives will be described elsewhere.

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