Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 8, pp. 1451-1452, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00205-3

Enantioselective Synthesis of Hydroxyalkylcyclopropanecarboxylic Acid Derivatives

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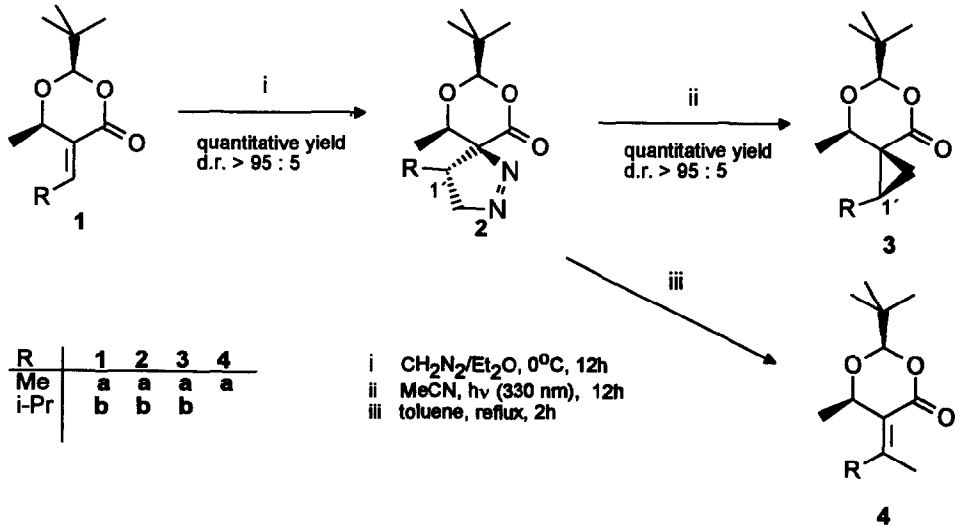
Abstract: Cycloaddition of diazomethane to enantiomerically pure 5-alkylidene-1,3-dioxane-4-ones **1** affords spiropyrazolines **2**. Upon irradiation these products loose N_2 giving cyclopropanes **3** that are spiro annellated to the 5-position of the 1,3-dioxane-4-one ring. Both transformations are highly stereoselective giving rise to essentially pure enantiomers in quantitative yields.

The two step synthesis by first addition of diazomethane to alkenes and further elimination of N_2 from the resulting pyrazolines is an useful access to cyclopropanes.[1] This method was also employed in the asymmetric synthesis of chiral spiro-cyclopropanes connected to heterocyclic compounds. For example 3-alkylidenediketopiperazines give the corresponding cyclopropanes which could be hydrolyzed to enatiomerically pure allocoronaric acid. [2]

Since homochiral 5-alkylidene-1,3-dioxane-4-ones, which are easily available[3] from naturally occuring (R)-3-hydroxybutanoic acid, gave highly stereoselective addition of organocuprates[3,4] or alkylradicals[5] to the C-C double bond, we expected such 3-hydroxy-butanoic acid derivatives **1** to be promising starting materials for asymmetric cyclopropane synthesis. Cycloaddition of diazomethane to 5-alkylidene-1,3-dioxane-4-ones **1** in ether at 0°C gave the expected pyrazolines **2**. The N_2 elimination from the cycloadducts **2** was achieved by irradiation at 330 nm. In all cases, both transformations gave only one detectable stereoisomer (according to ^{13}C-NMR) in quantitative yields. Attempts to eliminate N_2 from the pyrazolines **2** by catalytic methods (CuCl, $CuCl_2$ or $Ce(NH_4)_2(NO_3)_6$) or by heating (reflux in toluene) gave either no conversion or an elimination/isomerisation to branched 5-alkylidene-1,3-dioxane-4-one **4** respectively.The structure of all compounds **2**, **3**, and **4** is confirmed by elemental analyses and spectroscopic data (see Table). The stereochemical outcome of the cycloaddition/elimination could be determined by ^{1}H-NMR NOE experiments



R	1	2	3	4
Me	a	a	a	a
i-Pr	b	b	b	

of **3a** revealing the proximity of H in 6-position of the dioxanone ring to the methyl substituent (R = CH_3) of the cyclopropane ring rather than to the methylene group of the cyclopropane ring. Consequently the cycloaddition must have occured to the re-face of **1**. Spirocyclopropanes **1** are derivatives of hitherto unknown 2-substituted 1-(α-hydroxyethyl)-cyclopropanecarboxylic acids, which should be easily generated on acid hydrolysis.

	m.p./ °C	$[\alpha]_D$	^{1}H-NMR (300MHz, J/Hz) ($CDCl_3$)	^{13}C-NMR (75MHz) ($CDCl_3$)
2a	100-110 (dec.)	-277 (c 1, $CHCl_3$)	0.93 (d, 3H, CH_3-C1', J=7.4Hz); 0.99 (s, 9H, Me_3C); 1.09 (d, 3H, CH_3-6, J=6.4); 2.74 (qd, 1H, CH_{pyr}, J=9.0, 1.7); 4.10 (m, 2H, CH_{pyr}, CH-C6); 4.88 (dd, 1H, CH_{pyr}, J=9.1, 18.0); 5.10 (s, 1H, CH-C2)	13.4 (CH_3-C1'); 16.1 (CH_3-C6); 23.8 (CMe_3); 32.1 (CMe_3); 35.4 (CH-1'); 74.4 (CH-6); 85.9 (CH_{2pyr}); 97.0 (C-5), 109.2 (CH-2); 167.54 (C=O)
2b	100-111 (dec.)	-77,5 (c 2.1, $CHCl_3$)	0.91 (m , 9H, Me_2CH, CH_3-1C); 1.00 (s, 9H, 3 Me_3C); 1.49 (m, 1H, Me_2CH); 2.55 (pseudo q, 1H, CH $_{Pyr}$, J= 9.5); 3.80 (dd, 1H, CH_{Pyr}, J=17.8, 11.2); 4.12 (q, 1H, CH-6, J=6.4); 4.88 (dd, 1H, CH_{Pyr}, J=17.9, 9.3); 5.15 (s, 1H, CH - 2)	15.7 (CH_3-6); 23.6 (Me_2CH); 23.9 (Me_2CH); 23.8 (3 CH_3, Me_3C); 26.4 (Me_2CH); 35.5 (Me_3C); 45.6 (CH-1'); 73.6 (CH-6); 81.5 (CH_2); 95.2 (C-5); 109.3 (CH-2); 167.9 (C=O)
3a	oil	+56,6 (c 2.25, $CHCl_3$)	0.61 (dd, 1H, cycloprop, J=4,9; 7.8); 0.95 (s, 9H, Me_3C); 1.15 (d, 3H, CH_3-1', J=6,37); 1.18 (d, 3H, CH_3-6, J=6.3); 1.48 (m, 1H, CH - 1'); 1.76 (dd, 1H, cycloprop, J=4.5; 9.3); 4.00 (q, 1H, CH-6, J=6.3); 4.91 (s, 1H, CH-2)	13.3 (CH_3-1'); 18.9 (CH_2 cyclo-prop); 21.6 (CH_3-6); 23.8 ($CH_{cycloprop}$); 24.0 (Me_3C); 28.2 (C-5); 34.7 (Me_3C); 70.8 (CH-6); 105.7 (CH-2); 173.6 (C=O)
3b	oil	+ 80,7 (c 1, $CHCl_3$)	0.61 (dd, 1 H, cycloprop, J=5.1.; 7.7); 0.92 (s, 9 H, Me_3C); 1.00 (d, 6 H, 2 Me_2CH, J=3.1); 1.15 (d, 3 H, CH_3-1', J=6.2); 1.32 (m, 1H, CH-1'); 1.51 (m, 1 H, Me_2CH); 1.65 (dd, 1 H, cycloprop, J=4.8; 9.1); 4.02 (q, 1 H, CH-6, J=6.2); 4.97 (s, 1 H, CH-2)	17.5 ($CH_{2cycloprop}$); 21.8 (CH_3-1'); 22.3 (Me_2CH); 23.8 (Me_3C); 27.8 (Me_2CH); 29.0 (C-5); 34.6 (Me_3C); 37.8 ($CH_{cycloprop}$); 70.7 (CH-6); 105.4 (CH-2); 173.4 (C=O)
4a	68-69	--	0.91 (s, 9 H, Me_3C); 1,22 (d, 3 H, CH_3-6, J=6.3); 1.76 (s, 3 H, CH_3-1'); 2.04 (s, 3 H, CH_3-1'); 4.64 (s, 1 H, CH-2); 4.85 (q, 1 H, CH- 6, J=6.4)	21.1 (CH_3-6); 21.5 (CH_3-1'); 23.0 (CH_3-1'); 24.1 (Me_3C);34.2(Me_3C); 72.6 (CH-6); 104.2 (CH-2); 125.5 (C-1'); 147.2 (C-5); 166.3 (C=O)

Acknowledgement
We thank Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie for financial support.

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(*Received in UK* 9 *June* 1994)