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A CONVENIENT SYNTHESIS OF 5-SUBSTITUTED-4-HYDROXY-3,4,5,6-TETRAHYDRO-2H-PYRAN-2-ONES VIA A CHEMOSELECTIVE DIFFERENTIATION OF THE TWO ESTER FUNCTIONS OF DIMETHYL ACETONEDICARBOXYLATE

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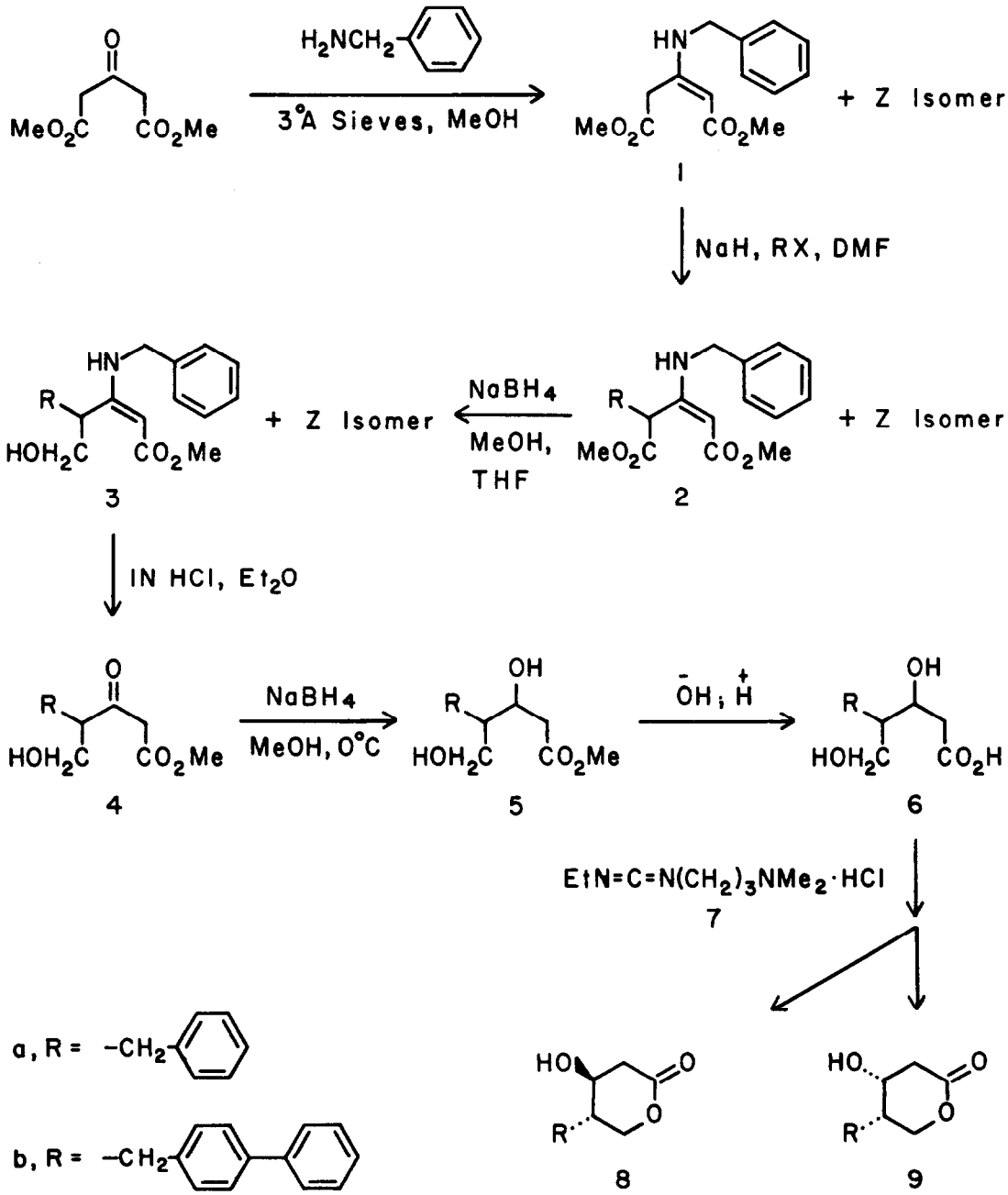
SUMMARY: Dimethyl acetonedicarboxylate formed the enamine 1 with benzylamine and thereby converted one of the carbomethoxy groups into a less electrophilic vinylogous urethane. Subsequent sequential alkylation of the active methylene moiety, chemoselective $NaBH_4$ reduction of the ester function, hydrolysis of the enamine moiety and reduction of the newly generated keto group afforded alcohols 5. Hydrolysis of the ester and lactonization gave the readily separable cis and trans lactones 8 and 9.

In the course of making inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), which catalyzes the rate limiting step and natural point of control of cholesterogenesis,[1] we had occasion to prepare 5- rather than the more common 6-substituted-4-hydroxy-3,4,5,6-tetra-hydro-2H-pyran-2-ones.[2] We opted to begin with symmetrical dimethyl acetonedicarboxylate. We reasoned that when an enamine is formed between dimethyl acetonedicarboxylate and benzylamine to afford Z:E mixture 1[3] (sieves, methanol), one of the methoxycarbonyl groups is converted into a vinylogous urethane which renders that carbonyl less electrophilic and leaves the other carbonyl normal. The remaining active methylene group was found to readily undergo base-catalyzed alkylation (DMF, NaH) with alkyl bromides and iodides to give the Z:E mixture 2 without isomerization (75%).[3b] Although $NaBH_4$ usually does not reduce esters, previously we had found that this reduction does proceed slowly, particularly in methanol.[4] Such a mild reducing agent should be able to differentiate between the two kinds of carbonyls in 2. Accordingly the more electrophic normal ester carbonyl group was found to reduce chemoselectively with $NaBH_4$[5] to provide the alcohol Z:E mixture 3[3b] (88%) with only a trace reduction of the vinylogous urethane carbonyl. $LiBH_4$[6] in THF was found to be much less chemoselective. The enamine 3 was hydrolyzed in a stirred, two-phase ether-1 N HCl mixture (30 h, RT)[7]. The resulting ketone 4 was reduced with $NaBH_4$ to give the erythro, threo compounds 5 accompanied by a small


H2NCH2
3°A Sieves, MeOH
+ Z Isomer
1
NaH, RX, DMF
NaBH4
MeOH, THF
+ Z Isomer
+ Z Isomer
3
2
IN HCl, Et2O
NaBH4
MeOH, 0°C
OH; H
4
5
6
EtN=C=N(CH2)3NMe2·HCl
7
a, R = -CH2
b, R = -CH2
8
9

amount of lactone. The mixture was hydrolyzed with hydroxide, acidified and lactonized with diimide 7 to give a nearly 1:1 mixture of trans and cis lactones 8 and 9 (54% overall yield from 3). The two isomers were readily separated by flash chromatography.

The stereochemistry of trans isomer 8a[8] is readily assigned based upon the width of the axial carbinol CH signal exhibited as a broad multiplet (23 Hz) centered at δ 3.98 (equatorial hydroxyl) and a broad multiplet (18 Hz) at δ 2.19 for the axial CH to which the equatorial benzyl group is attached in the 5-position of the ring. The equatorial disposition in the trans isomer was confirmed by a single crystal X-ray analysis of 8b which indicated an equatorial attachment of both substituents and a quasi chair conformation of the lactone ring. In addition to the narrower band width for the equatorial carbinol CH signal of the cis isomer 9a (8Hz) centered at 4.08, the axial hydroxyl in this cis isomer caused a 0.30 ppm downfield shift in the axial proton in the 6-position when compared to the trans isomer. This is due to a 1,3-diaxial deshielding by the hydroxyl group in accord with the 0.47 ± .1 ppm shift found for cyclohexanol.[9] Thus, a method for differentiating the ester functions of dimethyl acetondicarboxylate coupled with a novel chemospecific ester reduction has led to a convenient synthesis of novel 5-substituted lactones.

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3. a) Although the Z:E ratio varies, it does not effect the results. The Z:E ratio used in these experiments was 84:16, mp 52-54°C, as determined by the pairs of ^{1}H NMR signals: C4 methylene at δ 3.24 and 3.99; benzyl CH_2, 4.47 and 4.24; vinyl, 4.64 and 4.80. These Z:E mixtures are easily handled as they migrate either as a single band or as very close double bands on chromatography (silica gel, CH_2Cl_2). b) 2a (2, E mixture) ^{1}H NMR (300 M Hz) ($CDCl_3$) δ 2.83 (1H, q); 3.05 (1H, d); 3.12 (1H, d); 3.55 (3H, s); 3.62 (3H, s); 3.66 (3H, s); 3.68 (3H, s); 4.17 (2H, d); 4.33 (1H, m); 4.68 (1H, s); 4.70 (1H, s); 5.54 (1H, t); (5.81 (1H, m); 7.0-7.4 (1DH, m) 3a (Z, E mixture) δ 1.64 (1H, t); 1.96 (1H, t); 2.19 (H, S); 2.68 (1H, dd) 2.78 (H, dd); 3.8 (2H, m); 3.6 (3H, s); 3.64 (3H, 5); 3.66 (3H, s); 3.68 (3H, s) 3.84 (1H, m); 4.15-4.31 (3H, m); 4.58 (1H, m); 4.65 (1H, s); 4.70 (1H, s); 6.11 (1H, m); 7.0-7.4 (10H, m).
4. Unpublished results obtained in this laboratory.

5. $NaBH_4$, (6g, 0.159 mole) was added in small portions over a 6 hour period to a stirred solution of 2 (7.3 mmole) in methanol THF (1:1;v:v;100 mL) at ice-water bath temperature. The reaction was worked up and resubmitted to the reduction conditions when TLC showed the reaction to be incomplete. TLC is used to monitor completion of the reaction.
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7. Stronger acid facilitated enamine hydrolysis but caused some lactonization. The keto lactone thus formed ionizes on treatment with $NaBH_4$ and other reducing reagents, and as the ion is unreactive toward reduction.
8. **8a**: ^1H NMR (300 MHz) ($CDCl_3$) δ 2.25 (1H, m); 2.5-2.7 (4H, m); 4.08 (1H, m); 4.22 (1H, DD, J = 5 Hz, 11 Hz); 4.46 (1H, t, J = 11 Hz); 7.1-7.4 (5 H, m). **9a**: ^1H NMR (300 MHz) ($CDCl_3$) δ 2.25 (1H, m) 2.6-2.8 (4H, m); 4.22 (1H, DD, J = 5 Hz, 11 Hz); 4.46 (1H, t, J = 11 Hz); 7.15-7.45 (5 H, m) 8a, mp = 89-91°C, 96, gum; 86, 163-165°C; 9b, 136-138°C. All new compounds gave satisfactory NMR spectral data, microanalysis and/or mass spectra except for the mixture 5 where only NMR was obtained.
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