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ACID CATALYZED INTRAMOLECULAR CONJUGATE ADDITION AS A ROUTE TO *trans* HYDRINDANE SYSTEMS

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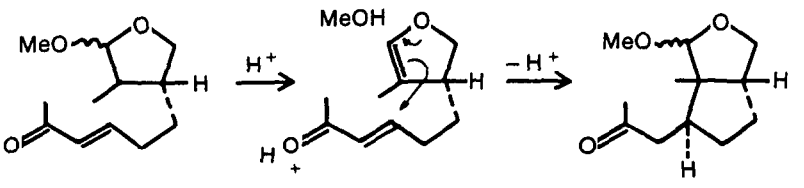
Abstract A stereocontrolled acid catalyzed intramolecular conjugate addition and its application in the enantioselective synthesis of *trans* hydrindanes are described

In this communication we wish to report an acid catalyzed stereocontrolled cyclization[2] (1 → 2) which might be applicable in the construction of chiral precursors for steroid synthesis

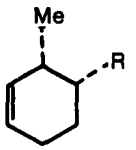


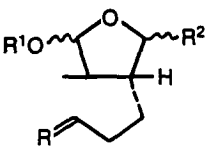
1 2

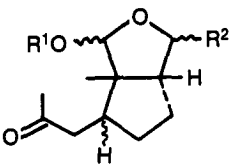
The starting material for these studies was the readily available cis-3-methyl-4-carboxy-cyclohexene (3)[3] The ester was reduced with $LiAlH_4$ and the resulting alcohol 4 was transformed to the enone 1 by a three step sequence Ozonolysis (CH_2Cl_2, -78°C, Me_2S workup) of the olefin 4 gave the lactol 5 which was treated with $(C_6H_5)_3P{=}CHCOCH_3$ (benzene, r t) to afford the enone 6 Compound 6 on stirring with methanol (CH_2Cl_2, Py^+Ts^-, r t) furnished the enone 1[5] in 51% yield from ester 3.

On treatment with catalytic TsOH in CH_2Cl_2, enone 1 was converted to the bicyclic product 2 in 70% yield The fact that the cyclization leading to 2 was very stereoselective with respect to the newly formed carbon-carbon bond was proved by its hydrolysis (aq acetone, HCl) to lactol 7 followed by oxidation (PCC, CH_2Cl_2) to the lactone 8[6] (72% overall yield), IR ($CHCl_3$) 1760, 1720 cm^{-1}, NMR ($CDCl_3$) δ 2 17, 2 16 (singlets, 3H), 1 32, 1 18 (singlets, 3H, ratio 1 10)

The proof that the major isomer corresponds to structure 2 follows from its conversion to



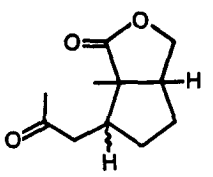




3 R = COOMe
4 R = CH_2OH
16 R = COOMenthyl

5 R = O, $R^1 = R^2 = H$
6 R = CHCOMe, $R^1 = R^2 = H$
1 R = CHCOMe, R^1 = Me, $R^2 = H$

2 R^1 = Me, $R^2 = H$
7 $R^1 = R^2 = H$



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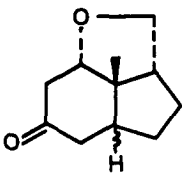

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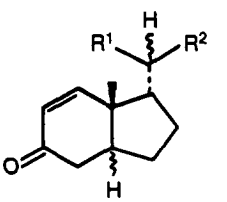
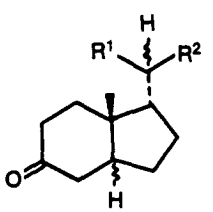
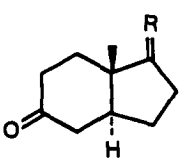


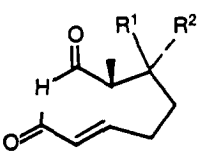
10 R^1 = H, R^2, = OCOMe



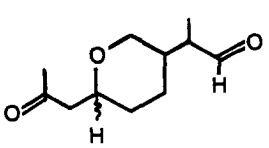
11 R^1 H, R^2 = OCOMe
12 R^1 = H, R^2 = OH
13 R^1 = H, R^2 = SePh(o-NO_2)



14 R = CH_2
15 R = O



17 R^1 = H, R^2 = CH_2OH



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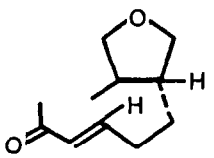
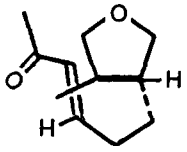
the known *trans* hydrindanone derivative 15.[2a] The lactol 7 on heating with KOH in aqueous methanol gave the tricyclic product 9 (60% from 2, two epimers by V P C ,[4] ratio 1 10). Compound 9 was transformed into the enone 10 (72%) by heating with acetic anhydride and TsOH in benzene Catalytic hydrogenation (EtOAc, Pd-C) of 10 and saponification of the resulting acetate 11 provided the alcohol 12 (88%) which on oxidative elimination[7] of the corresponding selenide 13[8] provided the olefin 14 (40% from 12) Ozonolysis (CH_2Cl_2, Me_2S workup) of 14 gave the *trans* diketone 15[2a] as the major product [9]

The predominance of the desired anti relationship of the angular methyl and hydrogen at the newly formed carbon-carbon bond in 2 can be rationalized by considering the transition states A and B [10]



A



B

The steric congestion in transition state B leading to *cis* isomer of 15[11] makes it less favorable than the alternative transition state A which favors the *trans* ring junction.

With the assumption that cyclization 1 → 2 will proceed without loss of optical activity, we decided to prepare the key intermediate 1 in optically active form. Diels Alder reaction of *trans* piperylene and R(-)menthyl acrylate (CH_2Cl_2, $EtAlCl_2$, -20°C) provided the ester 16[13] (70%) in 43% optical yield.[14] The transformation of compound 16 into the alcohol 12 proceeded as described for 3 → 12 Compound 12 had in fact been formed from 16 without loss of optical activity[14] Making use of the chiral acrylate derived from (-)-β-pinene[16] the optical yield of compound 1 could be improved to 55-60%

In conclusion, we have shown that the acid catalyzed intramolecular conjugate addition of systems such as 1 can be used to prepare optically pure[17] intermediates with controlled stereochemistry Compounds such as 10 can serve as valuable intermediates in the synthesis of chiral steriods.[18]

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References and Notes

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2 For related base catalyzed cyclizations see (a) Stork, G , Shiner, C S , Winkler, J D *J Am. Chem Soc* 1982, 104, 310, (b) Stork, G , Atwal, K , *Tet Lett* 1982, 2073, Stork, G , Winkler, J D , Saccomano, N S *Tet Lett* 1983, 465

3 Inukai, T , Kojima, T J *J. Org Chem.*, 1967, 32, 869. $EtAlCl_2$ in CH_2Cl_2 gives better yield (58% to alcohol 4) with 94% endo selectivity [3]

4. V P C. analysis was performed on SE-30 fused silica glass capillary column (25m x 0 24mm) using Packard Gas Chromatography Model 433.

5. The structure of compound 1 was proved by its hydrolysis (aq. acetone, HCl) followed by oxidation (PCC, CH_2Cl_2) of lactol 6 to the five-membered lactone which absorbs at 1747 cm^{-1} in I.R

6 V P C analysis[4] shows it to be a mixture, ratio 1 10, minor isomer elutes faster

7 Sharpless, K. B., Young, M W *J. Org. Chem.*, 1975, 40, 947

8. Grieco, P , Gilman, S , Nishizawa, M. *J Org Chem* , 1976, 41, 1485.

9. The minor product (0.4% at this stage) shows the same retention time[3] as an authentic sample of *cis*-isomer [2a]

10 The evidence for the intermediacy of A and B is circumstantial at this stage The cyclization (1 → 2) was unsuccessful in MeOH. The unstable intermediate (A,B), prepared by dehydration (MsCl/pyridine) of 6, refused to cyclize cleanly Additionally, if the ketoaldehyde 17 (open form of 1) is an intermediate (which could have been trapped with MeOH under acid catalysis) one would not expect high stereoselectivity during cyclization [11]

11 It is possible that *cis* product was formed from the open form (17) of 1 as acid catalyzed cyclization of such systems shows very little stereoselectivity.[12] Small amount (∿5%) of a byproduct 18 originating from 17 was actually isolated

12 Unpublished results from these laboratories

13 94% endo by V.P C analysis[4] of alcohol 4

14 The optical purity of compound 16 (and 12) was determined by preparing the Mosher ester[15] of alcohol 4 (and 12)

15 Dale, J A , Dull, D L., Mosher, H. S *J Org. Chem*, 1969, 34, 2543

16. Oppolzer, W *et al Helv Chim. Acta* , 1981, 64, 2802

17. Chiral cis-3-methyl-4-carboxy-1-cyclohexene (3, R = COOH) of course can be made by optical resolution of the (±) adduct: Monroe, J. D., Ph.D , thesis, Yale University, 1974 Since the sequence 4 → 12 proceeds without loss of optical activity, one can therefore obtain compound 10 in optically pure form.

18 Stork, G , Winkler, J. D , Shiner, C S *J. Am Chem Soc* 1982, 104, 3767

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