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CONTROLLED FUNCTIONALIZATION OF CYCLOHEPTA-1,3-DIENE: AN APPROACH TO THE (+) PRELOG-DJERASSI LACTONIC ACID.

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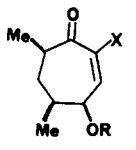
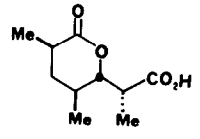
Abstract: The cycloheptenone (**1c**), a precursor to the (+) Prelog - Djerassi lactonic acid (**2**), has been synthesized stereoselectively from cyclohepta-1,3-diene.

The potential of seven-membered ring chemistry in natural product synthesis has previously been recognized by Stork[1], and White[2] both of whom successfully prepared cycloheptenones of structure (**1**) as intermediates for synthesis of the (+) Prelog-Djerassi lactonic acid (**2**).[3,4] Masamune has similarly utilized the seven-membered ring in a total synthesis of the macrolide antibiotic methymycin *via* (**2**) as a key intermediate.[5] However, most of these applications have not commenced with a simple seven-membered ring, but rather with a ring system which is better understood in terms of conformation/reactivity relationships, followed by conversion to the seven-membered system by, e.g., ring expansion.[1]





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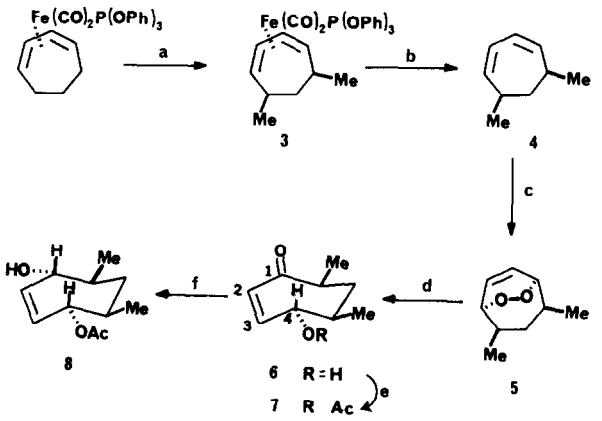
1 (a) X = Cl, R = CH_2OCH_3
(b) X = H, R = $Si(Me)_2Bu^t$
(c) X = H, R = COPh

We are currently investigating methods for stereoselectively introducing substituents onto a pre-formed seven-membered ring. Our attention was brought to the Prelog- Djerassi lactone as a synthetic target because of the *cis* 1,3 - relationship between the methyl substituents in intermediates (**1**). This stereochemistry is accessible using organoiron chemistry[6] as outlined in Scheme 1. The complex (**3**) is prepared by a simple sequence of operations in *ca* 90% overall yield. Decomplexation of (**3**) gave the stereochemically defined cycloheptadiene (**4**),[7] which now required controlled functionalization of the diene to give the desired cycloheptenones. Photooxygenation[8] of (**4**) gave a single endoperoxide which was assigned the structure (**5**), which in turn was converted directly to the hydroxy enone (**6**) on treatment with base, [80% overall yield from (**4**).] The stereochemistry of the derived acetate (**7**) was readily established by ^1H NMR spectroscopy,[7] which showed diaxial coupling (J = 8.8 Hz) between H(5) and H(4). Sodium borohydride reduction of (**7**) in the presence of cerium (III) chloride proceeded by addition of

hydride along the axial vector to give (**8**), the stereochemistry of which was again inferred from ^{1}H NMR coupling constants.[7] However, this does not correspond to the stereochemistry required for intermediates (**1**).



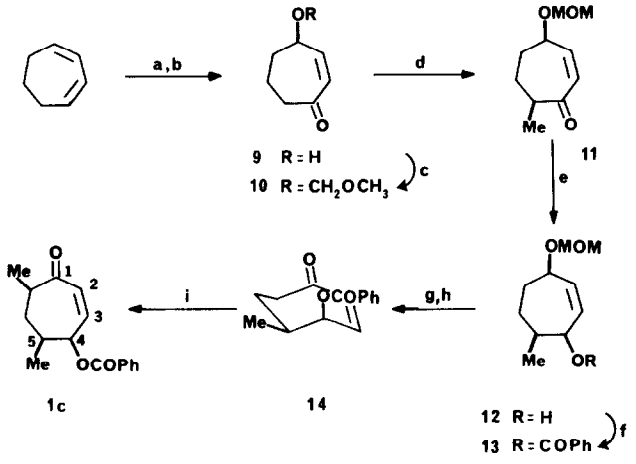
SCHEME 1

Reagents:

a: see ref.**6** , 90%, b: Me_3N-O, N,N-dimethylacetamide, 55°, 36h, 40%, c: O_2, tetraphenylporphin (cat.), 600W tungsten halogen lamp, CH_2Cl_2, rt, 1.5h, 90%, d: Et_3N (2.2 eq), CH_2Cl_2, reflux, 15h, 73%, e: Ac_2O (1.1 eq), pyridine (1.3 eq), CH_2Cl_2, rt, 12h, 98%, f: $NaBH_4$ (1.1 eq), methanolic $CeCl_3.7H_2O$ (0.4M), 0°C, 10 min, 98%.

There are a number of methods for inverting the stereochemistry of hydroxy substituents[9] which might be applied to intermediate (**8**) or derived compounds with the ultimate aim of obtaining, e.g., (**1c**) with correct relative stereochemistry. However, this was not pursued further, since we considered that a shorter, and chemically more interesting sequence of reactions could be developed. Cycloheptadiene was converted to the hydroxy enone (**9**) which was protected as its methoxymethyl (MOM) ether (**10**) (Scheme 2). From a consideration of the conformation[10] of the dienolate derived from (**10**), we anticipated reasonable stereocontrol during its alkylation. Deprotonation of (**10**) followed by methylation gave an approximately 3.5:1 mixture of stereoisomers. Analysis of subsequent reactions[11] indicated (**11**) to be the major product. Selective reduction of (**11**) occurred with a high degree of stereocontrol to give (**12**), which was readily converted in three steps to the enone (**14**). The cis stereochemical relationship between C(4) and C(5) substituents was evident from the ^{1}H NMR spectrum[7] which now showed a small (axial/equatorial) coupling between H(4) and H(5), in contrast to that observed for compounds (**7**) and (**8**). Methylation of the dienolate from (**14**) proceeded smoothly and with a high degree of stereocontrol (ca 10:1) to give the enone (**1c**), which showed ^{1}H NMR spectrum[7] comparable to that reported by White et al[2] for the similar cycloheptenone intermediate (**1b**), which was converted to the Prelog-Djerassi lactonic acid. Of particular note is the similarity in chemical shifts for the methyl groups in (**1c**) (δ1.02 and 1.12 p.p.m), (**1b**) (δ 0.98 and 1.10 p.p.m.) as well as the intermediate (**7**) (δ 1.02 and 1.12 p.p.m.), which is strongly indicative of the diequatorial nature of these substituents in all three compounds.[12]

In conclusion, readily available cyclohepta-1,3-diene[12] can be stereoselectively functionalized to give enones (**1c**) of (**7**), indicating the viability of using this compound as a precursor for a range of natural product molecules.



SCHEME 2

Reagents:

a O_2, tetraphenylporphin (cat.), 600W tungsten halogen lamp, CH_2Cl_2, rt, 1.5h, 100%, b: Et_3N (2.0 eq), CH_2Cl_2, rt, 6h, 95%, c: $CH_2(OMe)_2$ (large excess), P_2O_5, $CHCl_3$(P_2O_5 dried), rt, 10 min, 98%, d: LDA (1.1 eq), HMPA (2.0 eq), THF, -78°C, 1.5h, then MeI (1.2 eq) added at -78°C, 42%, e: $NaBH_4$ (1.1 eq), methanolic $CeCl_3.7H_2O$ (0.4M), 0°C, 10 min, 98%, f: PhCOCl (1.1 eq), pyridine (1.3 eq), CH_2Cl_2, rt, 12h, 98%, g: conc. HCl (cat.), MeOH, 55°C, 20 min, 90%, h: pyridinium chlorochromate (2.0 eq), CH_2Cl_2, rt, 10 min, 100%, i: LDA (1.1 eq), HMPA (2.0 eq), THF, -78°C, 1.5 h, then MeI added at -78°C, 40%.

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References and Notes

1) G. Stork and V. Nair, J. Am. Chem. Soc., 1979, 101, 1315.

2) J. D. White and Y. Fukuyama, J. Am. Chem. Soc., 1979, 101, 226.

3) Isolation and structure determination: R. Anliker, D. Dvornik, K. Gubler, H. Heusser and V. Prelog, Helv. Chim. Acta, 1956, 39, 1785; C. Djerassi and J. A. Zederic J. Am. Chem. Soc., 1956, 78, 2907; R. W. Rickards and R. M. Smith, Tetrahedron Lett., 1970, 1025.

4) Other synthetic approaches to (**2**): P. A. Grieco, V. Ohfune, Y. Yokoyama and W. Owens, J. Am. Chem. Soc., 1979, 101, 4749; P. A. Bartlett and J. L. Adams, ibid, 1980, 102, 337; D. J. S. Tsai and M. M. Midland, ibid., 1985, 107, 3915; R. E. Ireland and J. P. Daub, J. Org. Chem., 1981, 46, 470; B. Fraser-Reid and S. Jarosz, Tetrahedron Lett, 1981, 2533; D. A. Evans and J. Bartroli, ibid., 1982, 807; H. F. Chow and I. Fleming, ibid., 1985, 397.

5) S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georghiou and G. S. Bates, J. Am. Chem. Soc., 1975, 97, 3512; S. Masamune, H. Yamamoto, S. Kamata and A. Fukuzauo, ibid., 1975, 97, 3513.

6) A. J. Pearson, S. L. Kole and T. Ray, J. Am. Chem. Soc., 1984, 106, 6060.

7) All new compounds were obtained as racemic mixtures and were fully characterized by the usual spectroscopic methods. ^1H NMR data for selected intermediates is as follows:

(**7**): 1.02 (3H, d, J = 6.8 Hz), 1.12 (3H, d, J = 7.0 Hz), 5.17 (1H, ddd, J = 8.8, 3.7 and 1.6 Hz, CHOAc), 5.96 (1H, dd, J = 12.9 and 1.6 Hz, CO.CH=CH), and 6.21 (1H, dd, J = 12.9 and 3.7 Hz, CO.CH=CH). (**8**): 0.84 (3H, d, J = 6.9 Hz), 0.97 (3H, d, J = 7.0 Hz), 3.86 (1 H, bd, J = 9.0 Hz, CHOH), 5.00 (1H, bd, J = 9.7 Hz, CHOBz), 5.40 (1H, ddd, J = 12.2, 6.0 and 1.9 Hz) and 5.62 (1H, ddd, J = 12.2, 6.3 and 2.1 Hz). (**14**): 1.10 (3H, d, J = 6.9 Hz), 5.95 (1H, ddd, J = 4.7 and 1.95 Hz, CHOBz), 6.08 (1H, dd, J = 12.1, and 1.9 Hz), 6.51 (1H, dd, J = 12.1 and 4.34, 7.52 (3H, m, ArH) and 8.06 (2H, m, ArH). (**1c**): 0.97 (3H, d, J = 6.9 Hz), 1.11 (3H, d, J = 6.6 Hz), 5.95 (1H, m, CHOBz), 6.08 (1H, dd, J, 12.2, and 2.2 Hz), 6.45 (1H, dd, J = 12.2 and 3.9 Hz), 7.51 (3H, m, ArH) and 8.01 (2H, m, ArH).

8) R. W. Denny and A. Nickon, Org. Reactions, 1973, 20, 133.

9) E. J. Corey and S. Terashima, J. Org. Chem., 1972, 37, 3043.

10) Conformational analysis is discussed in the following communication.

11) Typically, an equatorial CH_3 group alpha to the ketone occurs in the NMR spectrum at around δ 0.99 p.p.m, while equatorial CH_3 not adjacent to a ketone occurs at δ 1.05 in cycloheptanones. An axial CH_3 not adjacent to ketone occurs at higher field, around δ 0.795. See: P. E. Pfeffer and S. F. Osman, J. Org. Chem. 1972, 37, 2425. Related ^{19}F NMR studies, see: E. S. Glazer, R. Knorr, C. Ganter and J. D. Roberts, J. Am. Chem. Soc., 1972, 94, 6026.

12) Cyclohepta- 1,3 -diene is commercially available but expensive. However, it is readily prepared by metal-ammonia reduction of the inexpensive cyclohepta-1,3, 5-triene, using a modification of the procedure described in : I. Pikulik and R. F. Childs, Can. J. Chem., 1977, 55, 251.

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