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A CATIONIC CYCLOPENTANNELATION

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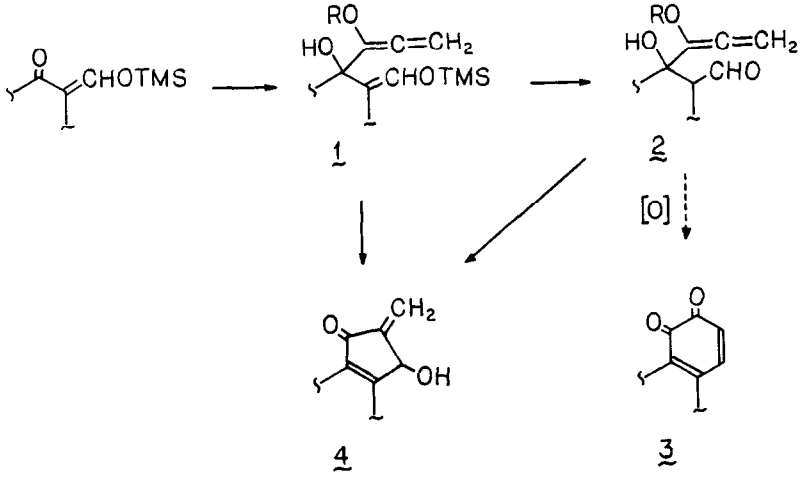
Abstract: The alkoxyallene adducts of O-trimethylsilyl hydroxymethylene ketones undergo a facile acid catalyzed cyclization to produce functionalized cyclopentenones in high yield.

We have recently disclosed a method for the preparation of catechol monoethers from α-methylene ketones.[1] Although the aromatic products were obtained in high yield it was postulated that a more convenient procedure for the preparation of ortho-quinones and catechols might be possible through the use of a more highly oxidized three carbon nucleophile. The addition of α-lithio-α-methoxymethylallene[2] to O-trimethylsilyl hydroxymethylene ketones produced adducts 1 which upon brief treatment with tetra-n-butylammonium fluoride in tetrahydrofuran of -78°C produced aldehydes 2. Epoxidation of either



of the two alkene groups of 2 could have led to an oxyallyl zwitterion[3] and a mechanism for its cyclization to an ortho-quinone 3 can be written. In the event, treatment of 2, derived from 4-tert-butylcyclohexanone, with m-chloroperoxybenzoic acid in dichloromethane

at 25°C led to a single product which was clearly not the quinone. The same product, subsequently identified as hydroxycyclopentenone 4, was obtained from Lewis acid treatment of 1. Adventitious m-chlorobenzoic acid evidently catalyzed the rapid conversion of 2 to 3.[4]

This extraordinarily simple pathway to densely functionalized cyclopentenones should prove to be synthetically useful. The similarity between the methylenomycins[5,6] and the structures afforded by this cationic cyclopentannelation is noteworthy. In order to probe the scope of this reaction a series of experiments was undertaken (Table 1). The reaction is not limited to O-trimethylsilyl hydroxymethylene ketones. Phenyl[7] (entry 5) or thiophenyl[8] (entry 6) substitution on the exo methylene group is tolerated by the reaction. Of particular interest with regard to the synthesis of the methylenomycins is the cyclization of 2-methylene-4-tert-butylcyclohexanone[9] (entry 7) which demonstrates that stabilization of the intermediate allylic cation derived from 1 is not necessary for the success of the reaction.

Ongoing research in our laboratories will attempt to demonstrate the utility of this serendipitous discovery for a short synthesis of methylenomycins. Representative experimental procedures follow.

Nucleophilic addition of α-lithio-α-methoxymethylallene. A solution of 4 mmol of n-butyllithium in 6 ml of a 1/1 mixture of ether and tetrahydrofuran (THF) was treated at -78°C with 5 mmol of methoxymethyl allenyl ether. Anion formation was presumed to be complete after 30-45 min.[2a] A solution of 1 mmol of the unsaturated ketone substrate[10] in 10 ml of ether/THF was added via cannula to the rapidly stirring lithioallene solution at -78°C. The progress of the reaction was monitored by thin layer chromatography. After ca. 30 min the reaction was quenched by addition of 3 ml of water. Upon warming to room temperature the reaction mixture was partitioned between ether and water. The ethereal layer was washed with water and brine and was dried ($MgSO_4$) and was concentrated to produce adducts 1 in 65-95% yield. Although the products of this reaction were stable to chromatography on silica gel, purification prior to cyclization was unnecessary.

Cationic cyclization. To a solution of 1 mmol of allene adduct in 10-15 ml of dichloromethane at 0°C was added boron trifluoride etherate (1 µl/5 mg) dropwise with rapid stirring. The progress of the reaction was monitored by thin layer chromatography. Upon completion (< 10 min) the reaction was quenched with 5% aqueous $NaHCO_3$ and was allowed to warm to room temperature. Partitioning between dichloromethane and water followed by drying ($MgSO_4$) and concentration produced the crude products which were purified by flash chromatography (ethyl acetate/hexane). Yields varied from 60-92%.

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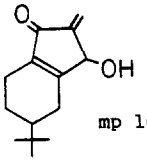
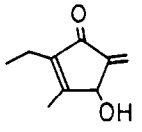
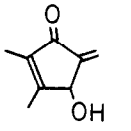
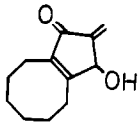
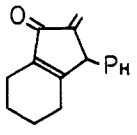
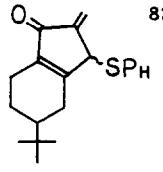
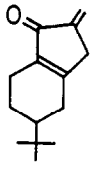
Table 1

		^{1}H nmr ($CDCl_3$, δ)	ir (ν_{max}, cm^{-1})	mass spectrum (m/e)
1.	 76%[a] mp 160-161°	[b]6.10 (d, J = 1.5 Hz, 1H, =CH) 5.62 (br s, 1H, =CH) 4.93 (br s, 1H, CHOH) 0.91 (s, 9H, tBu)	3400, 1700, 1640	220(p), 202(p-H_2O), 163(p-tBu), 136 Calcd for $C_{14}H_{20}O_2$ 220.1463 Found 220.1467
2.	 66-72%[d]	[b]6.11 (br s, 1H, =CH) 5.62 (br s, 1H, =CH) 4.85 (br s, 1H, CHOH) 2.28 (q, J = 7.6 Hz, 2H, CH_2) 2.11 (s, 3H, CH_3) 1.03 (t, J = 7.6 Hz, 3H, CH_3)	3450, 2950, 1710, 1650	152(p), 137, 134(p-H_2O), 123, 109, 95 Calcd for $C_9H_{12}O_2$ 152.0837 Found 152.0822
3.	 68%[d]	[c]6.05 (br s, 1H, =CH) 5.60 (br s, 1H, =CH) 4.85 (br s, 1H, CHOH) 3.38 (br s, 1H, OH) 2.08 (s, 3H, CH_3) 1.76 (s, 3H, CH_3)	3450, 2950, 1700, 1645	138(p), 124, 123, 122, 120(p-H_2O), 111, 110, 95 Calcd for $C_8H_{10}O_2$ 138.0681 Found 138.0669
4.	 80%	[c]5.95 (br s, 1H, =CH) 5.52 (br s, 1H, =CH) 4.84 (br s, 1H, CHOH) 3.56 (br s, 1H, OH) 1.39 (m, 8H, CH_2)	3450, 2900, 1710, 1645	192(p), 177, 175, 164, 149, 135 Calcd for $C_{12}H_{16}O_2$ 192.1150 Found 192.1142
5.	 75-78%[e]	[b]7.28 (m, 5H, ArH) 6.05 (d, J = 0.5 Hz, 1H, =CH) 5.09 (br s, 1H, =CH) 4.20 (br s, 1H, CHOH) 1.68 (m, 4H, CH_2)	2960, 1710, 1645	224(p), 196(p-CO), 187, 181, 167, 147(p-Ph), 135, 77 Calcd for $C_{16}H_{16}O$ 224.1201 Found 224.1198
6.	 82%	[b]7.24 (m, 5H, ArH) 6.14 (d, J = 1.6 Hz, 1H, =CH) 6.12 (d, J = 1.6 Hz, 1H, =CH) 5.59 (br s, 1H, =CH) 5.54 (br s, 1H, =CH) 4.43 (br s, 1H, =CH) 0.90 (s, 9H, tBu) 0.88 (s, 9H, tBu)	3400, 2980, 1710, 1590	312(p), 255(p-tBu), 204, 203(p-SPh), 202, 176, 137 Calcd for $C_{20}H_{24}OS$ 312.1548 Found 312.1559
7.	 56%[f]	[c]6.03 (d, J = 1.4 Hz, 1H, =CH) 5.32 (d, J = 1.6 Hz, 1H, =CH 3.08 (br s, 2H, CH_2) 0.90 (s, 9H, tBu)	2950, 1710, 1645	204(p), 176(p-CO), 148, 147(p-tBu), 117 Calcd for $C_{14}H_{20}O$ 204.1514 Found 204.1507

(a) Overall yields from the α-hydroxymethylene ketones. All materials were purified by flash chromatography. (b) Recorded at 300 MHz. (c) Recorded at 100 MHz. (d) The cyclization was performed at -78°C. The initially formed O-trimethylsilyl product was treated with tetra-n-butylammonium fluoride prior to workup. (e) Overall yield from benzalcyclohexanone. (f) Overall yield from the methiodide salt of 2-dimethylaminomethyl-4-tert-butylcyclohexanone.

References and Notes

1. M. A. Tius and A. Thurkauf, J. Org. Chem., 48, 3839 (1983).
2. (a) S. Hoff, L. Brandsma and J. F. Arens, Recl. Trav. Chim. Pays-Bas, 87, 916 (1968); (b) D. Gange and P. Magnus, J. Am. Chem. Soc., 100, 7746 (1978); (c) H. J. Reich and M. J. Kelly, J. Am. Chem. Soc., 104, 1119 (1982).
3. (a) M. Bertrand, J. P. Dulcere, G. Gil, J. Grimaldi and P. Sylvestre-Panthet, Tetrahedron Lett., 1507 (1976); (b) H. J. Reich, M. J. Kelly, R. E. Olson and R. C. Holtan, Tetrahedron, 39, 949 (1983).
4. Epoxidation of 2 with m-chloroperoxybenzoic acid in the presence of excess aqueous $NaHCO_3$ does not lead to 4. An epoxide, presumably derived from a zwitterionic intermediate, is formed instead. M. Tius and S. Ali, unpublished results.
5. Structure elucidation: (a) T. Haneishi, N. Kitahara, Y. Takiguchi and M. Arai, J. Antibiotics, 27, 386 (1974); (b) T. Haneishi, A. Terahara and M. Arai, J. Antibiotics, 27, 393 (1974); (c) J. Jernow, W. Tautz, P. Rosen and T. H. Williams, J. Org. Chem., 44, 4212 (1979). Several syntheses of methylenomycins have been reported. For examples see: (d) J. Jernow, W. Tautz, P. Rosen and J. F. Blount, J. Org. Chem., 44, 4210 (1979); (e) R. M. Scarborough, Jr., B. H. Toder and A. B. Smith, III, J. Am. Chem. Soc., 102, 3904 (1980); (f) Y. Takahashi, H. Kosugi and H. Uda, Chemistry Lett., 815 (1982); (g) A. B. Smith, III, and D. Boschelli, J. Org. Chem., 48, 1217 (1983); (h) E. Negishi and J. A. Miller, J. Am. Chem. Soc., 105, 6761 (1983), and references cited therein.
6. The ^1H nmr spectrum of entry 3 of Table 1 is very close to the reported[5a] spectrum for methylenomycin B. The ^{13}C nmr spectrum for the hydroxy compound of entry 3 was recorded: ($CDCl_3$, 75.6 MHz) δ 193.58, 165.97, 147.72, 141.85, 114.89, 72.82, 12.98, 7.84.
7. The substrate was prepared by base catalyzed condensation of benzaldehyde with excess cyclohexanone in ethanol.
8. R. E. Ireland and J. A. Marshall, J. Org. Chem., 27, 1615 (1962).
9. (a) J. L. Roberts, P. S. Borromeo and C. D. Poulter, Tetrahedron Lett., 1621 (1977); (b) T. A. Bryson, G. H. Bonitz, C. J. Reichel and R. E. Dardis, J. Org. Chem., 45, 524 (1980).
10. The preparation of O-trimethylsilyl hydroxymethylene ketones has been described: M. A. Tius and S. Ali, J. Org. Chem., 47, 3163 (1982).

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