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Conversion of 2-Heptenolides into Substituted Oxocene Systems. Its Application to the Synthesis of (+)-Lauthisan

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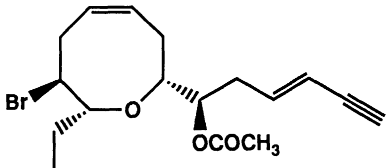
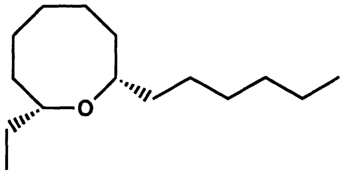
2-Heptenolide was smoothly transformed into the α,β,γ,δ-dienol triflate, which was reacted with lithium dialkylcuprates to afford α-alkylated oxocenes in good yields. The methodology was applied effectively to the synthesis of (+)-lauthisan.

Since past two decades ago, more than fifty compounds including halogenated eight-membered ether ring systems have been isolated from marine algae, *Laurencia* species.1) These could be structurally attractive synthetic targets. Since our first total synthesis of (±)-laurencin (1), the most representative compound, in laborious and lengthy steps,2) many synthetic groups have continued to develop various methodologies aimed to 1.3) However, no papers have been reported on the second synthesis of 1. We now disclose the preliminary results of the more effective synthetic procedure toward 1 and its related natural products, and their application to the synthesis of (+)-lauthisan (2).4)

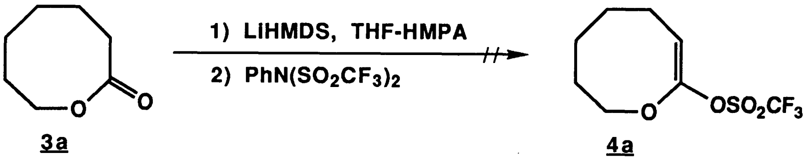


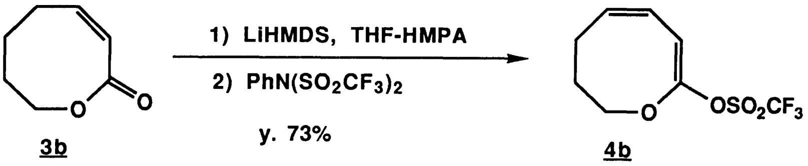
laurencin (1)



lauthisan (2)

We have recently reported that lactone enolates generally give rise to substituted cyclic ethers via enol triflates.5) However, only eight-membered lactone 3a led to no production of the desired cyclic ether 4a, resulting in oligomerization. The results seem to be due to transannular reaction between the lactone oxygen and a proton at 4-carbon. Accordingly, in order to avoid the reaction, we changed to use 2-heptenolide (3b) as the starting material. The reaction proceeded as anticipated to yield the

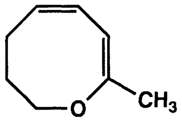
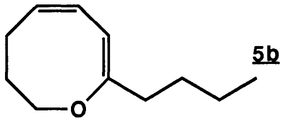
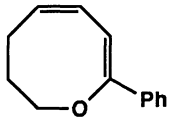
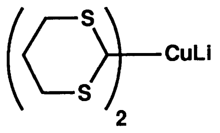
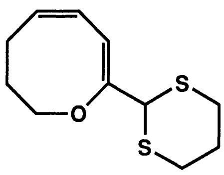




crude dienol triflate 4b in 73% yield. The compound 4b was smoothly coupled without further purification with lithium dialkylcuprates to give the corresponding α-alkylated oxocenes in good yields (Table 1).

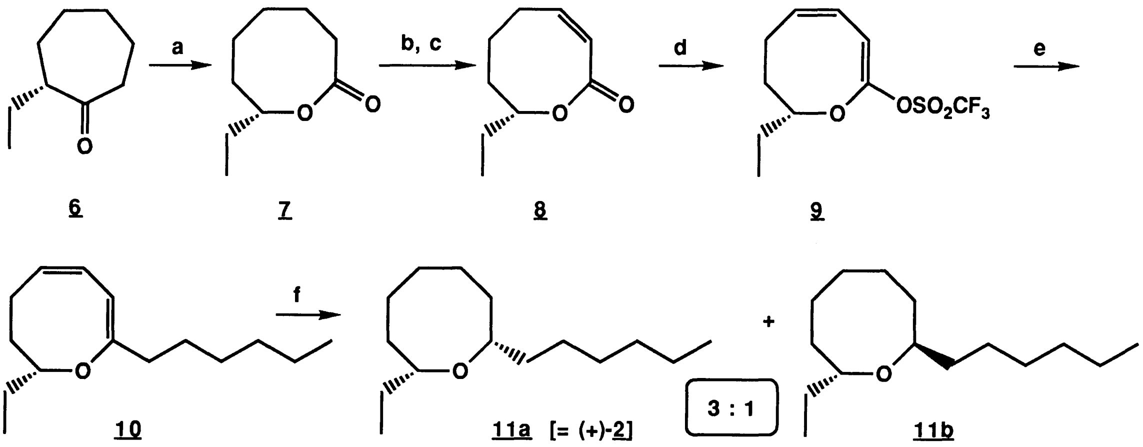
The present methodology was then applied to the synthesis of (+)-2[4)] (Scheme 1). The synthesis was commenced with the known compound, (*R*)-2-ethylcycloheptanone (6).[6)] The compound 6 was oxidized with *m*-chloroperoxybenzoic acid to afford (*R*)-7-ethylheptanolide (7), $[\alpha]_D^{24}$ -33.8° (c 0.87, $CHCl_3$),[7)] in 86% yield. Treatment of 7 with butyldimethylsilyl

Table 1. Conversion of 2-heptenolide dienol triflate (4b) into oxocenes

Run	R_2CuLi	Product	Yield/%
1	Me_2CuLi	 5a	61
2	Bu_2CuLi	 5b	82
3	Ph_2CuLi	 5c	82
4		 5d	74

trifluoromethanesulfonate and diisopropylethylamine in tetrahydrofuran (THF) at -15 °C for 16 h gave cyclic silyl ketene acetal in a quantitative yield,8) which, on oxidation with allyl methylcarbonate and a catalytic amount of palladium acetate in acetonitrile under reflux for 6 h,9) was transformed into (R)-7-ethyl-2-heptenolide (8), mp 53-54 °C and $[\alpha]_D^{25}$ +23.5° (c 1.02, $CHCl_3$), in 82% yield. The compound 8 was converted to the crude dienol triflate 9 in 60% yield, which was immediately reacted with lithium dihexylcuprate in a 5:1 mixture of THF and ether at -20 °C for 12 h to afford (R)-8-ethyl-2-hexyl-6,7-dihydrooxocene (10), $[\alpha]_D^{22}$ +234.0° (c 0.70, $CHCl_3$), in 63% yield. Finally, the compound 10 was hydrogenated in the presence of 10% palladium-carbon in THF under 1 atm at room temperature to give a 3:1 mixture of epimeric saturated compounds in 78% yield, which was separated by preparative thin layer chromatography over silica gel into 11a and 11b. The major product 11a,10) $[\alpha]_D^{22}$ +6.3° (c 0.13, $CHCl_3$),11) was identical with the authentic sample of (+)-lauthisan in all respects, while the minor product 11b, $[\alpha]_D^{24}$ +23.0° (c 0.05, $CHCl_3$), was found to be 2-epi-*trans*-lauthisan from the spectral data.12) The present synthesis of (+)-2 involves 6 steps from the known compound 6 and the overall yield amounts to 15%.13)

These results would be valuable as providing a new general procedure for the synthesis of various marine natural compounds with medium-sized cyclic ether ring systems including laurencin (1).



Reagents and conditions: a) mCPBA, CH_2Cl_2, 86%; b) TBSOTf, i-Pr_2NEt, THF, -15 °C, 95%; c) allyl methylcarbonate, $Pd(OAc)_2$, CH_3CN, 83%; LiHMDS/THF-HMPA, $PhN(SO_2CF_3)_2$, 60%; e) Hex_2CuLi, THF-ether, 63%; f) 1 atm H_2, 10% Pd/C, THF, room temp, 78%.

Scheme 1. Synthesis of (+)-lauthisan.

References

1) Cf., K. L. Erickson, "Constituents of Laurencia," in "Marine Natural Products, Chemical and Biological Perspectives," ed by P. J. Scheuer, Academic Press, New York (1983), Vol. 5, Chap. 4, pp. 131-257.

2) A. Murai, H. Murase, H. Matsue, and T. Masamune, Tetrahedron Lett., 1977, 2507; T. Masamune and H. Matsue, Chem. Lett., 1975, 895; T. Masamune, H. Matsue, and H. Murase, Bull. Chem. Soc. Jpn., 52, 127 (1979); T. Masamune, H. Murase, H. Matsue, and A. Murai, ibid., 52, 135 (1979).

3) L. E. Overman and A. S. Thompson, J. Am. Chem. Soc., 110, 2248 (1988), and references cited therein.

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6) D. Enders and H. Eichenauer, Chem. Ber., 112, 2933 (1979); D. Enders, "Asymmetric Synthesis," ed by H. Morrison, Academic Press, New York (1984), Vol. 3, Chap. 4, pp. 275-339; J. S. Clark and A. B. Holmes, Tetrahedron Lett., 29, 4333 (1988).

7) Compound 7 was treated with sodium methoxide in methanol and then converted into the corresponding MTPA ester with (R)-MTPA. The ^{1}H NMR analysis revealed that the ester has the optical purity of 91% e.e.

8) This new procedure for silyl ketene acetal is very mild and widely applicable: K. Tsushima and A. Murai, unpublished results.

9) I. Mikami, K. Takahashi, I. Shimizu, T. Kimura, and J. Tsuji, Tetrahedron, 42, 2971 (1986).

10) 11a: MS, m/z 226 (M^+, 0.26%), 208 (1.4), 197 (8.7), 141 (18.4), 123 (25.6), 97 (57.3), 83 (57.8), 69 (65.5), and 55 (100); IR ($CHCl_3$), 2932, 2856, 1464, 1380, 1088, and 994 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ3.42 (1H, m), 3.33 (1H, m), 1.27-1.78 (22H, m), 0.93 (3H, t, J=7.3 Hz), and 0.88 (3H, brt, J=6.8 Hz).

11) The reported value is $[\alpha]_D^{28}$ +5.3° (c 0.95, $CHCl_3$) for lauthisan.[4)]

12) 11b: MS, m/z 226 (M^+, 0.1%), 208 (2.5), 197 (7.7), 141 (22.5), 123 (55.3), 109 (23.2), 97 (41.5), 95 (42.4), 83 (47.1), 81 (72.5), 69 (57.7), 67 (65.8), 55 (100), and 41 (56.3); IR ($CHCl_3$), 2932, 2856, 1460, 1380, 1262, 1206, 1128, and 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ3.58 (1H, m), 3.52 (1H, m), 1.28-1.64 (22H, m), 0.91 (3H, t, J=7.3 Hz), and 0.88 (3H, brt, J=6.8 Hz).

13) Very recently, the first synthesis of (+)-2 was reported: H. Kotsuki, Y. Ushio, I. Kadota, and M. Ochi, J. Org. Chem., 54, 5153 (1989).

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