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Intramolecular Dipolar Addition of Carbonyl Ylides. Studies of Substituted Bicycloundecanones.

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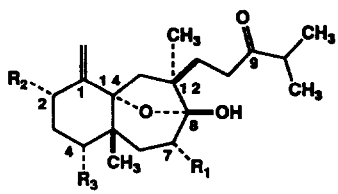
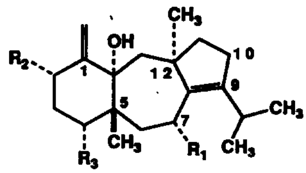
Summary: A synthetic route toward the secodolastanes is reported. The key transformations are derived from the [3 + 2]-intramolecular cycloaddition of a 3-oxidopyrylium ylide. Reductive cleavage of the tricyclic ether 15 yields the bicycloundecanone nucleus 19 of these terpenes.

The dolastanes are a family of marine terpenes which has recently grown to include cervicol acetate (1), linearol (2), [redacted] which have culminated in synthesis of the secodolastane skeleton 19 as a general strategy toward these unique natural products.





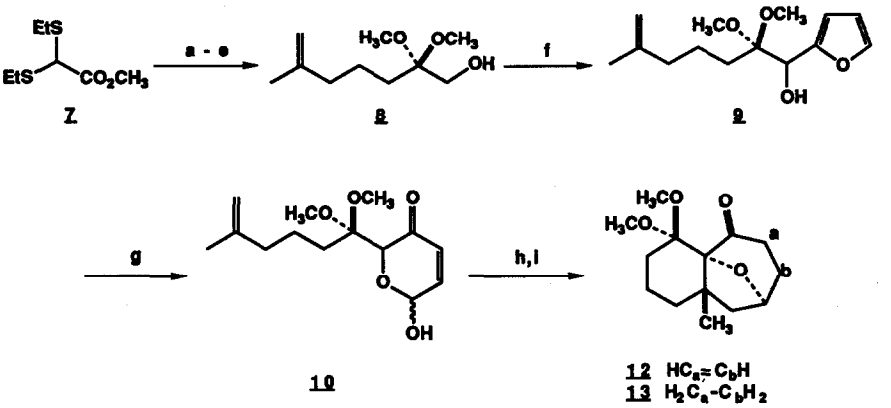
1 R_1 = OAc; R_2 = R_3 = H
2 R_2 = OH; R_1 = R_3 = H
3 R_3 = OH; R_1 = R_2 = H

4 R_3 = OH; R_1 = R_2 = H
5 R_1 = OH; R_2 = R_3 = H
6 R_2 = OH; R_1 = R_3 = H

Our investigations had sought to utilize the intramolecular dipolar addition of an appropriately functionalized cyclic carbonyl ylide with a terminal alkene as an efficient route to the *trans*-fused [5.4.0]bicycloundecanone nucleus of these terpenes. Sammes and others have reported the intramolecular cycloadditions of 3-oxidopyrylium ylides.[5,6] At the outset of our program, these studies lacked the relevant functionalization as required in our four-carbon tether (at C_1). Very recently Wender[6] and Padwa[7] have demonstrated additional examples of this elegant dipolar addition process. Our pathway to the prerequisite dihydropyranone 10, and formation of the tricyclic ether 13 is summarized in Scheme I.

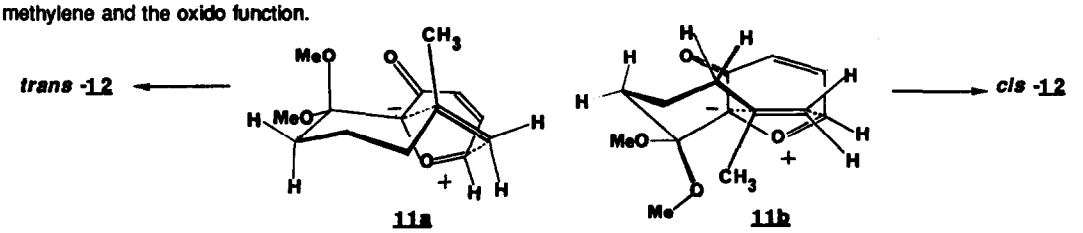
Alkylation of the *bis* ethylthio ketal of methyl glyoxalate[8] with 5-bromo-2-methyl pentene followed by reduction and ketal exchange provided 2,2-dimethoxy-6-methyl-6-hepten-1-ol in 34% overall conversion. Difficulties encountered upon scale-up of the ketal exchange reaction were avoided by initial silylation of the primary hydroxy group.[9] Swern oxidation of 8 followed by the *in situ* addition of 2-lithiofuran circumvented the need to isolate an unstable aldehyde, affording the furfuryl alcohol 9. Protocol widely utilized in carbohydrate chemistry allowed for oxygenation of the furan ring via addition of singlet oxygen at -78 °C with a reductive quench by dimethylsulfide leading to the precursor dihydropyranone 10.[10] Acetylation at 0 °C was followed by *in situ* elimination of acetic acid in methylene chloride with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) upon warming to room temperature, generating the intermediate 3-oxidopyrylium ylide 11. The ensuing stereoselective intramolecular cycloaddition afforded 83-93% isolated yields of a single unsaturated ketone 12 (mp 99-100 °C).[11]

Scheme I



(a) KH, THF/DMF (4:1), 0 ° → 22 °C, add bromopentene (70%); (b) LAH, Et_2O, 0 °C (80%); (c) tBDMSiCl, Et_3N, DMAP, CH_2Cl_2/DMF (1:1), 0 ° → 22 °C(88%); (d) $AgNO_3$, NCS, Collidine, THF/CH_3OH (1:1) -10 °C (87%); (e) nBu_4NF, THF (80%); (f) $(COCl)_2$, DMSO, Et_3N, THF, -78 ° → 0 °C, 45 min; -78 °C, add 2-lithiofuran precooled to -78 °C (78%); (g) O_2, Rose Bengal, CH_2Cl_2/CH_3OH (2:1), 40 w tungsten lamp, -78 °C; then DMS -78 ° → 22 °C (90%); (h) AcCl, pyr, CH_2Cl_2, 0 °C, then DBU, 22 °C (86%); (i) L-Selectride, THF, -78 °C (86%).

Conformational analysis of 11ab readily details reasons for the observed preferences for the trans-fused ring system. Two chair-like arrangements are illustrated. An equatorial disposition of the oxido substituent in 11a leads to the trans-fused product 12. However, the chair-like conformer 11b displays an unfavorable nonbonded interaction between the vinylic methyl and the developing axial methoxy (at C_1), as well as a serious steric interaction of the tether (C_4) allylic methylene and the oxido function.



Our assignment of relative stereoselectivity was unambiguously confirmed after treatment of 12 with basic hydrogen peroxide (H_2O; NaOH; MeOH, 0 °C; 92%). X-ray crystallographic analysis demonstrated exclusive formation of the corresponding α-epoxide of 12 (mp 117-118 °C).[12] Likewise, hydride reductions of 12 produced facile conjugate additions affording the saturated ketone 13.

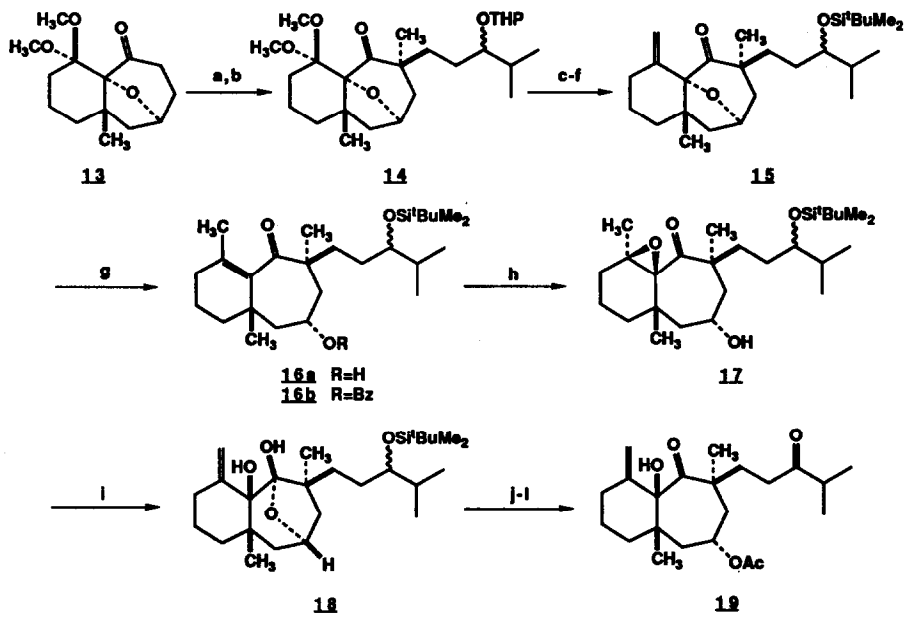
Numerous strategies for net 1,3-carbonyl transposition of the enone 12, including utilization of its corresponding α-epoxide and the related epoxy alcohol derivatives, have been unworkable. However, our studies with tricyclic ketone 13 have addressed the stereoselective formation of the C_9 quaternary carbon as well as the liberation of the C_7 hydroxy group. Details of these transformations are summarized in Scheme II.

Alkylation of 13 with 4-methyl-3-tetrahydropyranyloxy-1-iodopentane[13] followed by a second enolization and introduction of methyl iodide provided 14 as a single C_{12} diastereoisomer. Acid hydrolysis and selective nucleophilic attack at the less hindered carbonyl by methyl cerium afforded a ketone diol (as a 1:2 ratio of α/β C_1-OH diastereomers).[14]

Silylation of the secondary alcohol and elimination of the tertiary alcohols gave the desired exocyclic olefin 15.[15] Finally, smooth reductive cleavage of the oxo bridge of 15 was observed upon brief exposure to excess sodium naphthalenide. Immediate benzoylation of the crude product 16a gave 16b, facilitating chromatographic purifications and affording a temporary blocking group for subsequent epoxidation. Note that all attempts for cleavage of the bridging tetrahydrofuranyl ring via dissolving-metal reductions of ketones 13 or 14 were unsuccessful owing to an unsuitable alignment of the σ C_{14}-O bond and its adjacent C_{13} carbonyl.

Introduction of the final oxygen substituent provided a single oxirane in a completely stereoselective epoxidation. The relative configuration of this material was spectroscopically unassignable. Further reactions were undertaken with mild hydrolysis of the benzoate, and base-induced isomerization of the epoxide providing only the hemiketal 18. While we had suspected that oxygenation of 16b had produced the β-epoxide,[16] this was definitely proven by acetylation of 18 with subsequent deprotection and oxidation yielding the crystalline secodolastane 19 (mp 102-103 °C), as unambiguously confirmed by X-ray crystallographic analysis.[17] Further development of our scheme for synthesis of cervicol acetate is in progress.

Scheme II



(a) 5 eq LDA, THF, -78 °C, 40 min; then add 10 eq $ICH_2CH_2CH(CH_3)_2OTHP$, 10 eq DMPU, -78 ° → 22 °C (50%); (b) 5 eq LDA, THF, -78 °C then 10 eq CH_3I, 10 eq DMPU (95%); (c) $HClO_4$, CH_3OH/H_2O (4:1), heat (73%); (d) Premix 3 eq CH_3Li, 3 eq $CeCl_3$, THF, -78 °C; add ketone (79%); (e) tBDMSiCl, Et_3N, DMAP, CH_2Cl_2/DMF (1:2), 0 ° → 22 °C (90%); (f) $SOCl_2$, pyr, CH_2Cl_2, -10 ° → 22 °C (77%); (g) NaNaphthalenide (0.5 M in THF) added to 15 (0.01 M in THF), aqueous workup; then BzCl, DMAP, Et_3N, CH_2Cl_2 (77%); (h) mCPBA, CH_2Cl_2, 0 ° → 22 °C then; LiOH, $THF/CH_3OH/H_2O$ (4:4:1), 0 → 22 °C (87%); (i) 10 eq $LiNEt_2$, Et_2O (72%); (j) Ac_2O, pyr, CH_2Cl_2, 0 ° → 22 °C (97%); (k) nBu_4NF, THF, 0 ° → 22 °C (80%); (l) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ° → 0 °C (93%).

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9. Direct ketal exchange of 2,2-bis(ethylthio)-6-methyl-6-hepten-1-ol proceeded in good yields for small scale (less than 1.0 gram) experiments. However, the starting alcohol is extremely viscous and retains water after silica gel chromatography, thus giving rise to considerable amounts of the corresponding ketone under multigram-scale exchange conditions. Flash chromatography of the much less polar *tert*-butyldimethylsilyl ether solved this problem. The exchange process was necessitated owing to the competing oxidation of thioethers via singlet oxygen as demonstrated to us by the reactivity of the readily prepared dithiane corresponding to 8 (Scheme I). Also ketal exchange using the dithiane analog of 9 was unsuccessful due to the inherent instability of these furfuryl alcohols to Lewis acids.
10. Achmatowicz, O.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A.; *Tetrahedron*, **1971**, *27*, 1973. Our photolysis was readily conducted on a 20 gram scale. Singlet oxygen was the only reagent which succeeded in selectively oxidizing the furan ring without concomitant attack at the terminal olefin. Graziano, M.L.; Iesce, M.R.; Carli, B.; Scarpati, R. *Synthesis*, **1983**, 125.
11. Originally we had undertaken our [3 + 2]cycloaddition by heating the preformed acetate of 10 in DMSO with Hünigs base at 140 °C (83%) in accord with previous literature. However, as also noted by Wender and co-workers (ref. 6), we observed that our cyclizations occurred upon standing at room temperature.
12. Our structure assignment of the α-epoxide from enone 12 was confirmed by single crystal X-ray diffraction study of a colorless cubic crystal at -155 °C. All atoms were located and refined to final residuals of $R_{(F)}$ = 0.030 and $R_{W(F)}$ = 0.034. Complete crystallographic data are available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 88131.
13. This primary iodide was prepared from 3-benzyloxypropanol and isopropyl magnesium chloride using standard transformations. Allen, E.E. Ph.D. Dissertation, Indiana University (1988).
14. Our cyclohexanone substrate was prticularly susceptible to unwanted enolization with methyllithium or Grignard reagent. Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763.
15. Small quantities (5-10%) of the corresponding endocyclic olefin were also obtained and purified by silica gel chromatography. This material proved to be a poor substrate for the reductive cleavage of the tetrahydrofuranyl ring.
16. Similar diastereofacial C=C selectivity has been observed for electrophilic reagents in efforts towards dolastanes. Paquette, L.A.; Lin, H.-S.; Belmont, D.T.; Springer, J.P. *J. Org. Chem.* **1986**, *51*, 4807.
17. Structure assignment of 19 was confirmed by single crystal X-ray diffraction of a colorless crystal at -155 °C. All atoms were located and refined to final residuals of $R_{(F)}$ = .049 and $R_{W(F)}$ = .047. Complete crystallographic data are available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 90028.

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