Tetrahedron Letters, Vol. 34, No. 52, pp. 8553-8556, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Novel Cyclizations involving Vinyl Sulfones: Stereoselective Construction of Perhydroazulenes and *trans*-Hydrindanes.

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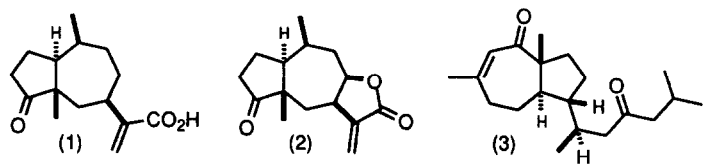
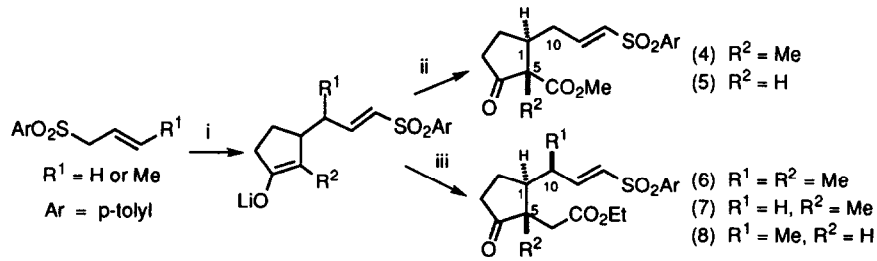
Abstract: Anionic species formed by treatment of vinyl sulfones with hydridoaluminates were trapped intramolecularly by esters to provide six- and seven-membered cyclic ketosulfones, exemplified by the stereoselective construction of *trans*-hydrindanes and of perhydroazulenes. This led to formal syntheses of confertin and damsinic acid.

Annelations occupy a central role in molecular construction,[1] and new methods which lead to synthetically versatile functional arrays are particularly valuable.[2] In an exploitation of conjugate additions of nucleophiles to vinyl sulfones,[3] intermediate sulfone-stabilised anions formed by use of carbon nucleophiles have been trapped intramolecularly by alkyl halides to form cyclopentane[4] and cyclohexane[5] rings. We now report that six and seven membered carbocyclic rings may be constructed by intramolecular acylation (by esters) of intermediate anionic species formed by reaction of vinyl sulfones with hydridoaluminates. The products are synthetically versatile β-ketosulfones. The reduction of vinyl sulfones to saturated sulfones by complex hydrides is well established,[6] but the trapping of intermediate anionic species by carbon electrophiles has not been described previously.

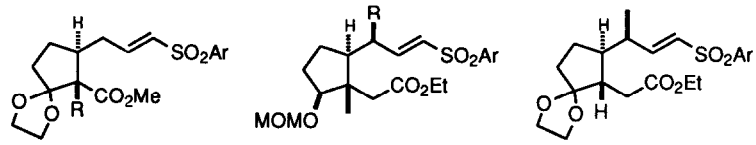


The reactions were developed during an investigation of stereoselective routes to pseudoguaianolides of the ambrosanolide family,[7] such as damsinic acid (1) and confertin (2), and other perhydroazulene derivatives such as Reiswigin A (3), which shows potent anti viral activity.[8] For other syntheses, routes to *trans*-hydrindane derivatives were also required. These routes commenced with the construction of cyclopentanone derivatives (4)-(8) by a method based on the work of Haynes et.al. (Scheme 1).[9, 10]



Scheme 1. i, a, BuLi-THF, -78 → 0 °C, b, 2-cyclopentenone or 2-methyl-2-cyclopentenone, 1 min.;
ii, $NCCO_2Me$ (for R^1 = H) -78°C; iii, a, Ph_3SnCl (1.5 equiv.) 30 min., b, ICH_2CO_2Et (3 equiv.) 18h:.
Yields from 2-cyclopentenone or 2-methyl-2-cyclopentenone:- (4) (60%); (5) (50%); (6) (73%); (7) (61%); (8) (55%).

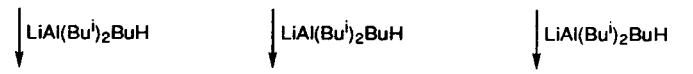
The *trans* orientation about C-1 - C-5 (pseudoguaianolide numbering) in (4)-(8) is a consequence of 1,2-asymmetric induction,[11] and the highly stereoselective formation of the chiral centre at C-10 in (6) and (8) is a feature of Michael additions of allyl sulfone lithio anions to cyclopentenones.[9] The ketones (4)-(8) were subsequently converted into their derivatives (9)-(13) respectively by routine procedures.[12,13]

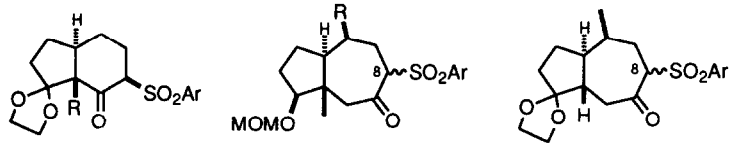


(9) R = Me
(10) R = H

(11) R = Me
(12) R = H

(13)

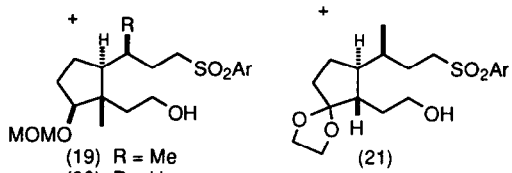




(14) R = Me
(15) R = H

(16) R = Me
(17) R = H

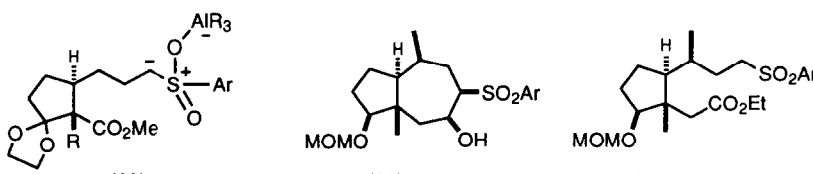
(18)



(19) R = Me
(20) R = H

(21)

Treatment of (9) with lithium butyldi-isobutylhydridoaluminate[14] in hexane-THF for 15 minutes at room temperature gave the ketosulfone (14) (95%).[15] Similar treatment of (10) gave the ketosulfone (15) almost quantitatively (NMR), but the unoptimized yield of analytically pure material was moderate (46%) because of chromatographic difficulties associated with its insolubility. Clearly, anionic species generated by conjugate addition of hydride to the vinyl sulfone readily underwent intramolecular acylation, and reduction of the ester did not compete. The precise nature of the anionic species is not clear, but we tentatively formulate them in the ylidic form (22) in view of the known propensity of aluminium-derived Lewis acids to complex with sulfonyl oxygen.[16]



(22)

(23)

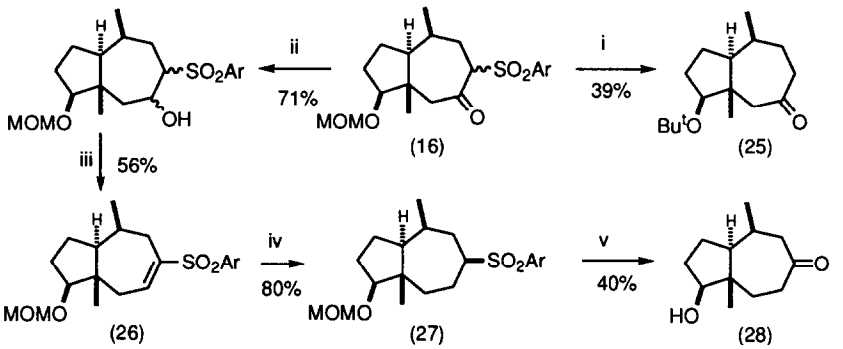
(24)

The formation of seven-membered rings by this method was less efficient, because reduction of the ester competed with intramolecular acylation. Nevertheless, cyclization still proceeded in synthetically useful yields. Treatment of (11), (12), and (13) with lithium butyldi-isobutylhydridoaluminate in the above manner gave respectively the ketosulfones (16) (58%), (17) (61%) and (18) (53%) together with the corresponding hydroxysulfones (19) (24%), (20) (37%), and (21) (37%) from which they were readily separated by

chromatography. In contrast to the completely stereoselective formation of (14) and (15), the ketosulfones (16)-(18) were obtained as a 2:1 mixture of epimers at C-8 according to NMR.

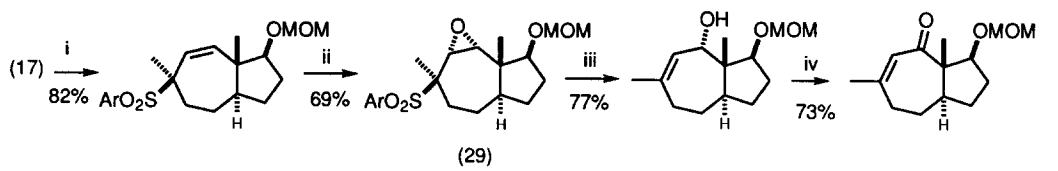
Lithium butyldi-isobutylhydridoaluminate emerged as the best reagent to effect clean cyclization after a study of the behaviour of (11) with a number of hydridoaluminates. With lithium aluminium hydride in ether at 0°C for 20 minutes, (11) gave (16) (15%), (19) (46%) and the cyclic hydroxy sulfone (23) (25%). The hydroxy sulfone (23) was not formed when $LiAl(OMe)_3H$, $LiAl(OMe)_2H_2$, or $LiAl(OEt)_2H_2$ were used, in THF, the sole cyclic product being the ketosulfone (16) (40-56%), which was, however, accompanied by unidentified by-products from which it was difficult to separate. With $LiAl(OBu^t)_3H$ in boiling ether for 24 h the only product (24) (85%) was that of conjugate reduction of the vinyl sulfone.

These remarkably easy cyclizations led to formal syntheses of damsinic acid (1) and confertin (2), reported total syntheses of which involve the key intermediates (25)[17] and (28)[18] respectively. These ketones were prepared from (16) by straightforward transformations (Scheme 2), which included the completely stereoselective reduction of the vinyl sulfone (26), and the oxidation[19] of the derived sulfone (27) by treatment in sequence with lithium di-isopropylamide and oxodiperoxymolybdenum(pyridine)(N,N-dimethyl-3,4,5,6-tetrahydropyrimidinone (MoOPD).[20]



Scheme 2. *Reagents*: i, a, 6% Na/Hg, NaH_2PO_4, MeOH ; b, HCl, MeOH ; c, $CH_2{=}CMe_2$, H^+ ; ii, $NaBH_4$; iii CH_3SO_2Cl, pyridine, DBU; iv, $LiAlH_4$:; v, a, LDA, MoOPD.; b, HCl, MeOH.

The usefulness of this new method of constructing cyclic ketosulfones was further demonstrated by transformations which we are currently exploiting for a synthesis of Reiswigin A (3) (Scheme 3). These reactions, which included the slow (96h) but efficient reduction of the epoxysulfone (29) by Kocienski's method,[21] all proceeded with complete stereoselectivity.



Scheme 3 *Reagents*: i, a, NaH - MeI; b, $LiAlH_4$; c, $SOCl_2$ - pyridine:
ii, MCPBA; iii, 6% Na/Hg - THF - MeOH; iv, $BaMnO_4$.

The scope and limitations of this new mode of cyclization, together with precise details of its mechanism, remain to be clarified, but we consider it provides a useful way of making hydrindane and perhydroazulene derivatives.

Acknowledgements: We thank the SERC for studentships (to M.W.J. M. and S.S) and Glaxo Group Research for a Research Studentship (to N.C.O.T.)

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10. All new compounds were characterized by IR, ^{1}H NMR, and MS or elemental analysis.
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12. The ketones (4), (5) and (8) were treated with ethane-1,2-diol and *p*-toluenesulphonic acid (cat.) in boiling benzene, with removal of water (Dean-Stark) to give (9) (76%), (10) (71%) and (13) (81%) repectively. Treatment of (6) and (7) with sodium borohydride in methanol gave the 4β alcohols stereoselectively, which were treated with dimethoxymethane, *p*-toluenesulphonic acid (cat.), and lithium bromide (cat.) (cf. ref. 13) to give (11) and (12) respectively (both in 70% overall yields from the respective ketones).
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14. Prepared by mixing equimolar solutions of di-isobutylaluminium hydride and butyllithium in hexane at -78 °C, and dilution with dry THF to give a 0.4M or 0.75M solution of lithium butyldi-isobutylhydridoaluminate (cf. Kim, S.; Ahn, K.H.; Chung, Y.W., *J. Org. Chem.*, 1982, **47**, 4581, who prepared the analogous reagent from t-butyllithium, which we found less satisfactory.).
15. The procedure for preparing (14) was typical . A stirred solution of the vinyl sulphone (9) (520 mg, 1.32 mmol) in dry THF (40 ml) was treated with lithium butyldiisobutylhydroaluminate (3.5 ml of a 0.75M solution in hexane-THF, 2.63 mmol) at room temperature under argon. After 15 min methanol (3 ml) was added, followed by water (3 ml). The solvent was evaporated under reduced pressure, and the residue treated with ethyl acetate (70 ml) and an EDTA solution (100 ml of a 5% solution) and stirred vigorously overnight. The organic layer was washed with water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave the product (14) (460 mg, 95%), m.p. 191-192 °C (needles from ethyl acetate), ν_{max} 1729 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, J 8.5 Hz), 7.33 (2H, d, J 8.5 Hz), 4.12 (1H, m, acetal), 4.06, (1H, m, acetal), 4.06 (1H, dd, J 12.5 & 6 Hz, $ArSO_2CH$), 3.93 (1H, m, acetal) 3.82 (1H, m, acetal), 2.45 (1H, m), 2.45 (3H, s, Ar-CH_3), 2.33 (1H, m), 2.00 (2H, m), 1.88 (1H, m), 1.40 (1H, m) 1.07 (3H, s, CH_3); (Found: C, 62.3; H, 6.6; S, 8.7; m/z 364. $C_{19}H_{24}SO_5$ requires C, 62.6; H, 6.6; S, 8.8%; M^+ 364). The structure of this compound was confirmed by X-ray crystallographic analysis of the derived hydroxy sulfone.
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(Received in UK 11 October 1993; accepted 22 October 1993)