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CONVENIENT (Z)-ETHYLIDENECYCLOPENTANE ANNULATION SEQUENCES. TOTAL SYNTHESIS OF (±)-OPLOPANONE, (±)-8-EPI-OPLOPANONE, AND (±)-ANHYDRO-OPLOPANONE

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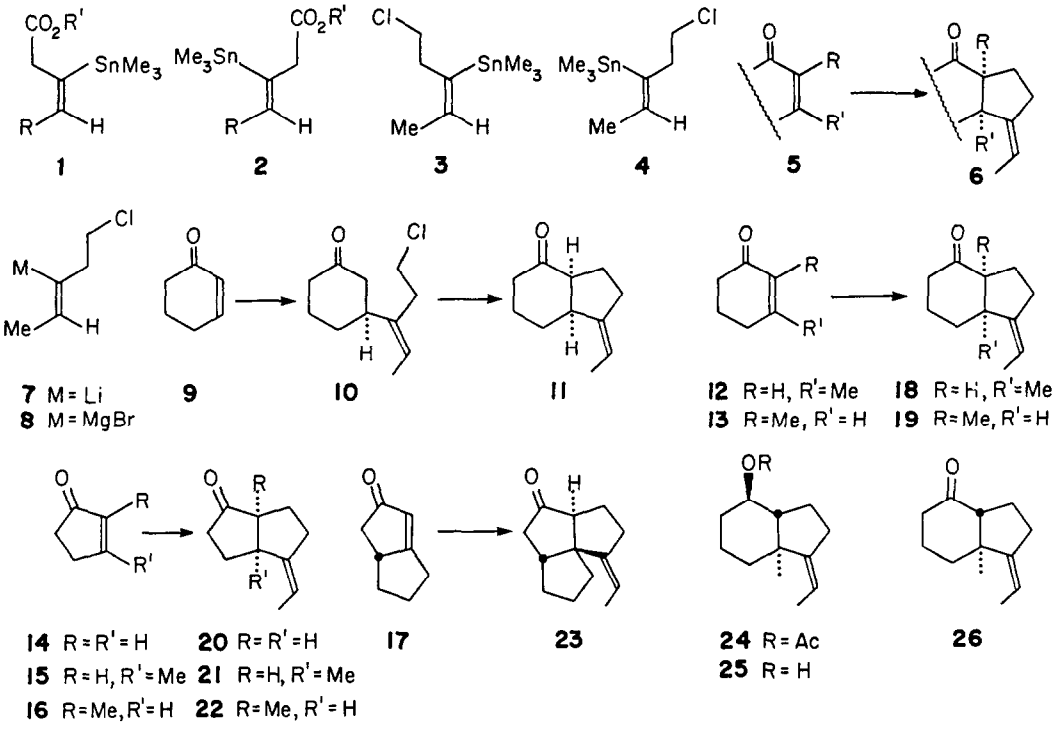
ABSTRACT: Conjugate addition [tetrahydrofuran (THF)-Et_2O, $CuBr \cdot Me_2S$, $BF_3 \cdot Et_2O$, -78°C] of the Grignard reagent 8 to the enones 9, 12-17, followed by base-promoted intramolecular alkylation of the resultant products, gives the (Z)-ethylidenecyclopentane annulation products 11, 18-23, respectively. This new annulation method is applied to the total synthesis of the oplopanane-type sesquiterpenoids 27, 28, and 38.

In a recent communication,[1] we described an efficient, stereoselective synthesis of alkyl (E)- and (Z)-3-trimethylstannyl-3-alkenoates (1 and 2, respectively) and noted that the geometric isomers 1 and 2 (R=Me, R'=Et) can be converted smoothly into the corresponding chlorides 3 and 4. We report herein the effective use of compound 4 in carrying out (Z)-ethylidenecyclopentane annulation reactions (generalized in 5 ⟶ 6) and describe the application of this new synthetic method to the total synthesis of the oplopanane-type sesquiterpenoids (±)-oplopanone (27), (±)-8-epi-oplopanone (38), and (±)-anhydro-oplopanone (28).

Transmetallation (MeLi, THF, -78°C, 20 min) of the vinylstannane 4 produced the lithio derivative 7, which, upon treatment with 1.2 equivalents of anhydrous $MgBr_2$, was converted into the Grignard reagent 8. Dilution of the solution (-78°C) with Et_2O, followed by successive addition of $CuBr \cdot Me_2S$ (0.3 equiv.), 2-cyclohexen-1-one (9) (1 equiv.), and $BF_3 \cdot Et_2O$ (1.2 equiv.)[2] gave, after a reaction time of 2 h and suitable workup, the conjugate addition product 10[3] (70%). Intramolecular alkylation (KH, THF, r.t.) of the latter material provided the bicyclic olefinic ketone 11 (78%).

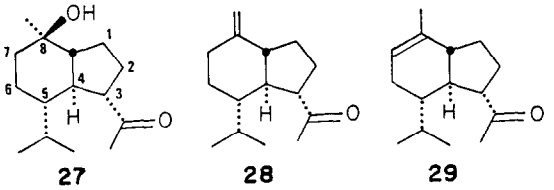
The generality of this interesting (Z)-ethylidenecyclopentane annulation sequence was demonstrated by the conversion of the enones 12-17 into the annulation products 18-23, respectively. In each case, a procedure identical with that outlined above was employed. The overall yields were typically about 50%. Interestingly, even the conjugate additions of the relatively hindered Grignard reagent 8 to the β,β-disubstituted enones 12, 15, and 17 were quite efficient.

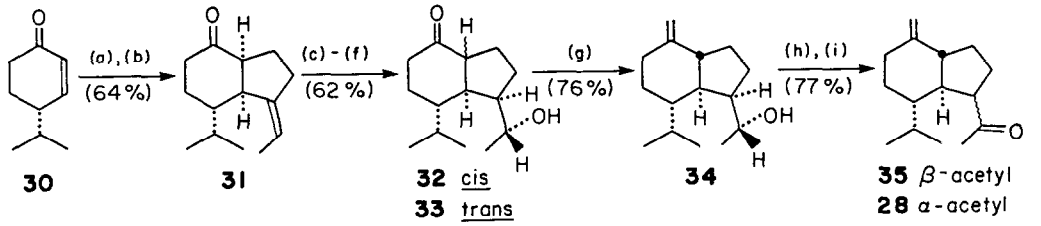
The constitution and relative stereochemistry of compound 18, which is structurally related to some recently prepared steroid CD-ring synthons, was shown conclusively as follows. Hydrolysis (K_2CO_3,MeOH) of the acetate 24[4] (one enantiomer), followed by oxidation ($C_5H_5N \cdot CrO_3 \cdot HCl$, NaOAc, CH_2Cl_2) of the resultant alcohol 25, provided the ketone 26 which was spectrally different from 18. However, treatment of 26 with KOH in EtOH-H_2O caused complete epimerization at the bridgehead position adjacent to the carbonyl group and



produced a ketone which exhibited ir and ^{1}H nmr spectra identical with those of our annulation product 18.

The structurally interesting sesquiterpenoid (-)-oplopanone, initially isolated from Oplopanax japonicus, was shown[5] to possess the constitution and absolute configuration shown in formula 27. Two total syntheses of (±)-oplopanone have been reported.[6,7] The olefinic ketones (-)-anhydro-oplopanone (28)[8] and (-)-α-oplopenone (29)[9] are also natural products, having been isolated from Euryops pedunculatus and Santolina oblongifolia, respectively. The substances 27-29 are three members of a small group of oplopanane-type sesquiterpenoids which are, formally, rearranged cadinanes.

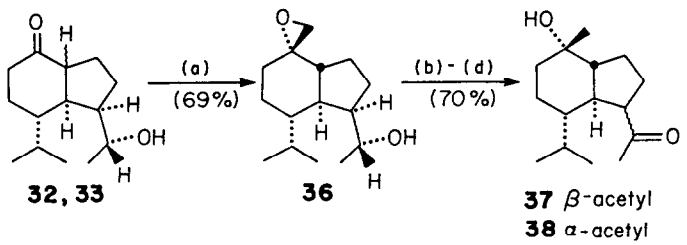




Scheme 1. (a) 8, CuBr·Me_2S, BF_3·Et_2O, THF-Et_2O, -78°C, 2 h (b) KH, THF, r.t. (c) $HOCH_2CH_2OH$, C_5H_5N·p-TsOH, C_6H_6 (d) BH_3·Me_2S, THF, r.t.; NaOH, H_2O_2, 40-50°C (e) C_5H_5N·p-TsOH, acetone-H_2O (f) NaOMe, MeOH, r.t. (g) $Ph_3P{=}CH_2$ (3 equiv.), DMSO, r.t. (h) C_5H_5N·CrO_3·HCl, CH_2Cl_2 (i) NaOMe, MeOH, 60°C, 24 h.

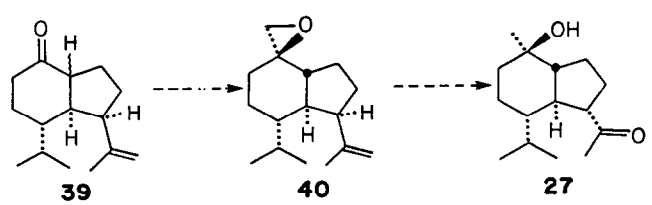
Examination of the structures of 27-29 indicates that the annulation method described above could play a key role in a short synthesis of these natural products. A total synthesis of (±)-anhydro-oplopanone (28) is outlined in Scheme 1. (Z)-Ethylidenecyclopentane annulation of 4-isopropyl-2-cyclohexen-1-one (30) provided, in 64% yield, the bicyclic ketone 31.[10] Conversion of 31 into the keto alcohol 32 proceeded in a straightforward manner. Equilibration (NaOMe, MeOH) of 32 produced a 1:3 mixture of 32 and the epimer 33, respectively. Importantly, the latter substance reacted with $Ph_3P{=}CH_2$ more rapidly than did 32 and, since the Wittig reaction was carried out under equilibrating conditions, the 1:3 mixture of 32 and 33 was converted primarily into the desired trans-fused olefinic alcohol 34 (76% yield after flash chromatography on silica gel). Oxidation of 34 and (slow!) equilibration of the resultant ketone 35 yielded a 7:93 mixture of 35 and (±)-anhydro-oplopanone (28). Fractional crystallization of this mixture from petroleum ether provided (77% from 34) pure 28, m.p. 68°C, which exhibited spectra identical with those of authentic (-)-anhydro-oplopanone (28).[8,11]

Treatment of the 1:3 mixture of 32 and 33 with dimethylsulfonium methylide[12] in DMSO-THF (see Scheme 2) gave the epoxide 36 (m.p. 92.5-93°C, 69% yield after flash chromatography), accompanied by two minor products. Reduction of 36 and oxidation of the resultant diol afforded the ketol 37 which, upon equilibration, provided a 7:93 mixture of 37 and (±)-8-epi-oplopanone (38) (m.p. 62°C, purified by flash chromatography and recrystallization from hexane-ether). The 400 MHz ^1H nmr spectrum of 38 was very similar to, but clearly different from, that of authentic (-)-oplopanone (27).[13]



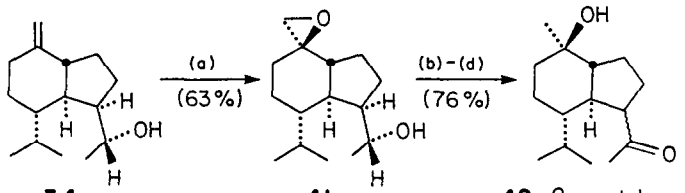
Scheme 2. (a) Me_3SI, $MeSOCH_2Na$, DMSO-THF, -5°C -> r.t. (b) $LiAlH_4$, Et_2O (c) $C_5H_5N{\cdot}CrO_3{\cdot}HCl$, CH_2Cl_2, NaOAc (d) NaOMe, MeOH, 60°C, 24 h.

It is pertinent to point out that, recently, Köster and Wolf[14] reported an efficient preparation of the ketone 39 (mixture of epimers). Treatment of this material with dimethylsulfonium methylide[12] (equilibrating conditions) was reported to give mainly the epoxide 40 which, upon subjection to an appropriate sequence of reactions ($LiAlH_4$ reduction, ozonolysis, and base-promoted equilibration), was claimed to provide (±)-oplopanone (27). However, the m.p. of this synthetic substance (63-64°C)[14] was quite different from those reported (101.5-102°C,[6] 97-98°C[7]) previously for (±)-27. It is evident from our work, summarized above (Scheme 2), that Köster and Wolf had actually prepared, not (±)-27, but (±)-8-epi-oplopanone (38).



A successful synthesis of (±)-oplopanone (27), starting from our synthetic intermediate 34, is summarized in Scheme 3. Thus, epoxidation of 34 via the corresponding bromohydrins[15]

gave, after chromatographic separation of the two resultant products, the desired epoxide 41 (63%, m.p. 91°C) along with a small amount (12%) of the epimeric substance. Reduction of 41 provided the corresponding diol (m.p. 117-118°C) which, upon oxidation, afforded the keto alcohol 42 (m.p. 68°C). Equilibration of the latter material, followed by fractional crystallization of the resultant mixture (42 and 27, 6:94, respectively), gave (±)-oplopanone (27, m.p. 99-100°C) in 76% yield from 41. Compound 27 exhibited spectra identical with those of natural (-)-oplopanone.[13]



Scheme 3. (a) NBS, H_2O-DMSO, r.t.; K_2CO_3, MeOH, r.t. (b) $LiAlH_4$, Et_2O (c) $C_5H_5N \cdot CrO_3 \cdot HCl$, CH_2Cl_2 (d) NaOMe, MeOH, 40-45°C, 36 h.

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REFERENCES AND NOTES

1. Piers, E.; Gavai, A.V. J. Chem. Soc., Chem. Commun., 1985, 1241. 2. Cf. Lipshutz, B.H.; Parker, D.A.; Kozlowski, J.A.; Nguyen, S.L. Tetrahedron Lett., 1984, 25, 5959, and references therein. 3. All compounds reported herein exhibited spectra in accord with structural assignments and gave satisfactory high resolution mass spectrometric molecular mass measurements. 4. Baggiolini, E.G.; Iacobelli, J.A.; Hennessy, B.M.; Uskokovic, M.R. J. Am. Chem. Soc., 1982, 104, 2945. We are grateful to Dr. Baggiolini for a generous sample of compound 24. 5. Takeda, K.; Minato, H.; Ishikawa, M. Tetrahedron, Suppl. No. 7, 1966, 219. 6. Caine, D.; Tuller, F.N. J. Org. Chem., 1973, 38, 3663. 7. Taber, D.F.; Korsmeyer, R.W. J. Org. Chem., 1978, 43, 4925. 8. Bohlmann, F.; Zdero, C. Phytochem., 1978, 17, 1135. 9. De Pascual-T., J.; Vicente, S.; Gonzalez, M.S.; Bellido, I.S. Phytochem., 1983, 22, 2235. 10. The stereochemistry of each of the synthetic intermediates given in Schemes 1-3 was assigned on the basis of literature precedent, predictions regarding steric approach control, conformational analysis, and/or ^1H nmr spectroscopy (coupling constants, difference NOE experiments, etc.). Details will be given in a full paper. 11. We thank Professor Bohlmann for a copy of the ^1H nmr spectrum of (-)-28. 12. Corey, E.J.; Chaykovsky, M. J. Am. Chem. Soc., 1965, 87, 1353. 13. We are very grateful to Dr. M. Matsumoto, Shionogi Research Laboratory, for a sample of (-)-27 and for copies of its ir and ^1H nmr spectra and to Professor Taber for copies of ir, ^1H nmr, and mass spectra of (±)-27. 14. Köster, F.-H.; Wolf, H. Tetrahedron Lett., 1981, 22, 3937. 15. Yamazaki, M.; Shibasaki, M.; Ikegami, I. Chemistry Lett., 1981, 1245.

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