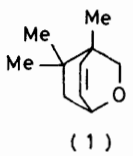
Syntheses of Two Naturally Occurring Monoterpenes with the Santolinyl Skeleton

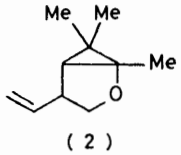
By **Derek V. Banthorpe** * and **Paul N. Christou**, Christopher Ingold Laboratories, University College, London WC1H 0AJ

Artemiseole, an ether isolated from *Artemisia tridentata*, has been proved to be 1,4,4-trimethyl-6-vinyl-3-oxabicyclo[3.1.0]hexane by an unambiguous synthesis in six steps from 1-chloro-2-methylpropene, and is thus an irregular monoterpene of the santolinyl class. The availability of 3,6,6-trimethyl-5,6-dihydro-2*H*-pyran as an unexpected minor product of one of the steps allowed an efficient eight-step synthesis from the chloro-compound of (*Z*)-5-ethylidene-5,6-dihydro-3,6,6-trimethylpyran-2-one to be carried out: this is an irregular monoterpene lactone from *Chrysanthemum flosculosum* that had previously been prepared only by a fifteen-stage process.

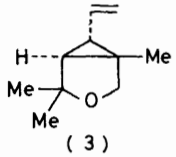
A MONOTERPENE ether from *Artemisia tridentata* (sagebrush) grown in the U.S.A. was initially given the structure (1) [1] but was re-assigned as structure (2) on the basis of re-interpretation of the spectral data.[2] However, it was subsequently found that the reported i.r. and ^{1}H n.m.r. spectra, and also the mass spectrum of the natural product, differed significantly from those of an authentic sample of (2).[3] Analysis of the ^{13}C n.m.r. spectrum of the natural compound, biogenetic arguments, and model experiments using possible biogenetic intermediates, led to the suggestion of a third structure (3), *i.e.* 1,4,4-trimethyl-6-vinyl-3-oxabicyclo[3.1.0]-



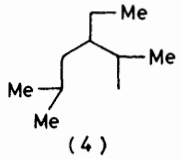
(1)



(2)



(3)



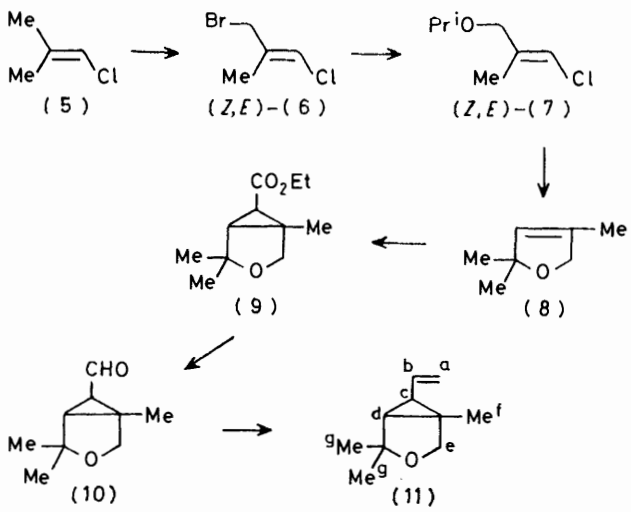
(4)

hexane, and the compound was named artemiseole.[4] This compound has the santolinyl skeleton (4) which is a type known to occur in other monoterpenes from *A. tridentata*.[4] Compounds (1)—(3) are all irregular; *i.e.* they abrogate the Biogenetic Isoprene Rule in not being derived in any obvious manner from geraniol or its biogenetic equivalent.

We here record an unambiguous synthesis of the ether that confirms the compound to have structure (3). In the event, one of the steps of the synthesis yielded an unexpected minor product that provided a convenient route to a monoterpene lactone, *i.e.* (*Z*)-5-ethylidene-5,6-dihydro-3,6,6-trimethylpyran-2-one, (18), which had been previously isolated from *Chrysanthemum flosculosum*.[5,6] This irregular monoterpenoid, which for brevity we shall refer to as chrysanthemum lactone, also has the santolinyl skeleton and has recently been unambiguously synthesised in poor yield in a fifteen-step process starting from ethyl α-bromobutyrate.[7]

RESULTS AND DISCUSSION

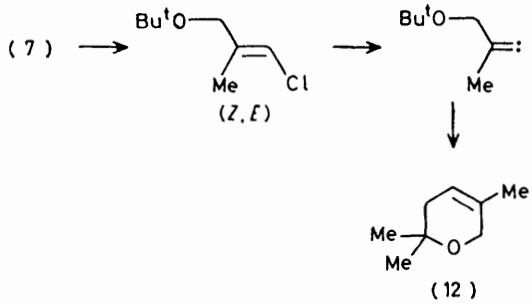
Artemiseole was synthesised in six stages from 1-chloro-2-methylpropene (5), Scheme 1. Yields of the



SCHEME 1

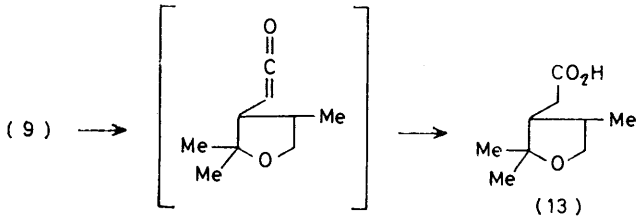
steps were 20—60% but the overall yield was only *ca.* 0.5%. 3-Chloro-2-methylpropene could be used as starting material but this resulted in the first step having a *ca.* five-fold lower yield.

Two points were of particular interest. The first was the formation of (12) together with (8) on treatment of (7) with sodium t-butoxide. The conversion (7) ⟶ (8)



is thought to involve a carbene as intermediate,[8] but previous analysis of the complex mixture of reaction products had not revealed the presence of (12).[8] It

seemed likely that under our conditions cross-etherification had occurred to yield the t-butyl ether, which then cyclised [*cf.* (7) ⟶ (12)]. Such reactions under basic conditions are uncommon,[9] but we have indeed checked that treatment of ethyl vinyl ether with base under the conditions used for the conversion (7) ⟶ (8) gave appreciable (*ca.* 25%) yields of t-butyl ethyl ether, and so the suggestion of cross-etherification in the step of the main synthetic route seems justified. Secondly, reduc-

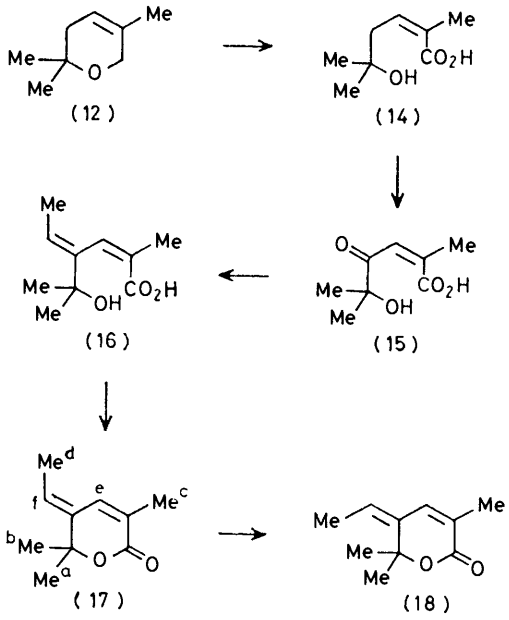


tion of (9) with >1 mol equiv. of sodium aluminium hydride resulted in the formation of the acid (13) as the major product rather than the desired aldehyde (10). This may be the result of the intermediate formation of a keten formed by expulsion of ethoxide ion from the ester (9) after attack by hydride ion on the cyclopropyl ring [*cf.* (9) ⟶ (13)]. Use of equimolar proportions of the reductant, however, resulted in the predominant formation of the desired product.

The final product, which we presumed from the unambiguous nature of the synthetic route to be 1,4,4-trimethyl-6-vinyl-3-oxabicyclo[3.1.0]hexane (11) correctly analysed as $C_{10}H_{16}O$, and had a mass spectrum that was identical with that of a sample of the natural product. The ^{1}H n.m.r. spectrum was superimposable on the spectrum of the latter save for slightly greater complexity in the multiplicity of the vinyl proton at δ 5.58 and of the signal due to the proton on the cyclopropane ring at δ 1.21. The i.r. spectra of the synthetic and natural products were also identical except for the presence of a few weak bands in the former that were absent in the latter. These slight differences were considered to reflect the circumstance that the natural product was a single stereoisomer (3), whereas our synthetic route must have led to a mixture of two isomers epimeric at C-6. Indeed, our synthetic product could be resolved into two closely separated components by capillary g.l.c. and analytical-scale t.l.c. using several stationary phases and solvent systems, but unfortunately these components could not be obtained pure by preparative-scale g.l.c. or t.l.c. or h.p.l.c. under several sets of conditions.

The ether could not be detected (by coupled g.l.c.–mass spectrometry) in oils from *A. tridentata* or in extracts from several other *Artemisia* species that were cultivated in England,[10] but Professor W. Epstein (Salt Lake City) kindly provided an authentic sample (*cf.* ref. 4), and co-chromatography of this with our product under a variety of conditions revealed that the minor component (36%) of the latter behaved identically with the natural product. The authentic sample was also used to compare its spectral properties with those of the synthetic material (see above). Our chosen synthetic route involved intermediates of proven (as judged by spectral properties) and expected structures; and additionally there was no obvious scope for rearrangement or other unexpected intruding reactions. Consequently, we claim to have shown beyond all reasonable doubt that the structure of the ether from *A. tridentata* is (11); and given the proven skeleton, the previous analysis of the spectra proves that the naturally-occurring isomer is (3).

The unexpected availability of (12), the structure of which was proven by ^{13}C and ^{1}H n.m.r. and mass spectrometry, enabled us to develop a convenient route to chrysanthemum lactone (18) in five steps from (12) or in eight steps from (5) (Scheme 2). Yields were 16 and



SCHEME 2

0.5%, respectively, for the two pathways. Points of note were; (*a*) the oxidation of (12) by SeO_2 to form (14) with exclusive attack at the least hindered methylene group; and (*b*) the unique introduction of the ethylidene group in the stereochemical situation as in (16), again due to steric control. Lactonisation of (16) gave exclusively the *E*-lactone, which is reported to be converted by photolysis into its equilibrium mixture with the naturally occurring *Z*-lactone (*cf.* ref. 7). The ^{1}H n.m.r., i.r., and mass spectra of our sample of the *E*-lactone agreed with those reported for the synthetic material,[7] and photolysis of this by the technique described previously [7] led to a mixture of the *E*-lactone with another compound (3 : 7 w/w). The newly produced compound was confirmed to be the *Z*-isomer by comparison [capillary g.l.c. and analytical-scale t.l.c. (several systems)] with an authentic sample of the natural product kindly provided by Professor H. Uda (Tohoku University).

The assignment of the naturally occurring lactone as

Z was based[7] on double-resonance ^{1}H n.m.r. We confirmed these assignments by the use of Eu(fod)$_3$ as a shift reagent for ^{1}H n.m.r. Up to a mol ratio (reagent: substrate) of 1 : 1, a clear pattern of shifts revealing a first-order spectrum was achieved, which indicated (although a quantitative analysis was not made) that the reagent complexed to the carbonyl oxygen, and that the lactone formed by cyclisation of (16) was indeed the *E*-isomer, and that the natural product was the corresponding *Z*-isomer.

EXPERIMENTAL

Techniques.—^{1}H N.m.r. spectra (10% v/v in deuteriochloroform or deuterioacetone) were measured at 100 MHz with tetramethylsilane (δ 0.00) as internal standard. ^{13}C N.m.r. spectra were obtained with a Varian XL-100 spectrometer (25.2 MHz) on solutions (20% v/v) in deuteriochloroform. Fourier-transform spectra were obtained with ^{1}H-decoupling and an accumulation time of 0.4 s with 10^4 transients. This gave a spectrum with 2 048 real data points *i.e.* ±2.5 Hz (±0.1 p.p.m.): standard off-resonance spectra were obtained by using single-frequency decoupling at δ −15. Mass spectra were obtained with a modified Metrovik MS9 instrument operating at 70 eV ionising potential, with the injection chamber at 70 °C. Preparative g.l.c. was carried out on a 2.5 m × 1 cm (outside diameter) column of 15% (w/w) Carbowax M on 60—80 mesh Supasorb at 120—160 °C with N_2 carrier gas (5—8 l h^{-1}). Analytical determinations were made on either a 16 m × 0.2 mm capillary column of Carbowax 20M (WCOT) with N_2 carrier gas (0.3 l h^{-1}) at 100 °C, or a similar SE30 capillary column under the same conditions. Final products were shown to be homogeneous (>99%, except for the occurrence of epimers, see above) by use of these columns and by t.l.c. on (*a*) silica gel H; (*b*) cellulose; (*c*) silicic acid; and (*d*) alumina with (*i*) ethyl acetate–hexane (15 : 85 v/v); (*ii*) ethyl acetate–benzene (20 : 80 v/v); (*iii*) ethyl acetate–toluene (20 : 80 v/v); (*iv*) ether–toluene (10 : 1 v/v) as solvents.

Artemiseole.—1-Chloro-2-methylpropene (37 g) was converted into (*Z*, *E*)-1-chloro-2-methyl-3-bromopropene by treatment with *N*-bromosuccinimide and benzoyl peroxide in CCl_4:[11] during work-up the solvent was removed below 30 °C/90 mmHg under N_2 in order to reduce decomposition. The product (6), b.p. 38—40 °C/60 mmHg, yield 33 g (47%) [*E*-isomer (67%); δ 1.93 (3 H, s), 3.94 (2 H, s), and 6.26 (1 H, s)] *Z*-isomer (33%) had additional bands at δ 4.08 and 5.95, and was very lachrymatory. (*E*, *Z*)-(6) (32.8 g) was then converted into (*E*, *Z*)-(7) [yield 16 g (59%), b.p. 94—95 °C/110 mmHg; δ 1.10 (6 H, d), 3.52 (1 H, septet), 1.75 (3 H, s), 4.13 (*Z*) and 3.85 (*E*), (2 H, s), and 6.08 (*E*) and 5.95 (*Z*) (1 H, m)] by treatment with Pr^{i}OH–Pr^{i}ONa.[8] This mixture (16 g) on reaction with Bu^{t}OK–THF under N_2[8] yielded a mixture (10 g) of six main products which was separated by h.p.l.c. (Waters Prep-500 model) on silica gel (2 × 30 cm) that had been equilibrated with EtOAc–CH_2Cl_2 (1 : 9) (2 l) followed by EtOAc (2.5 l) and was eluted with EtOAc–CH_2Cl_2 (5 : 95). Two components were isolated (R_t 2.8 and 4.0 min): the former was compound (8), yield 20%; $\nu_{max.}$ 3 025, 2 995, 1 685, 1 485, 1 390, 1 350, 1 215, 1 140, 1 110, 1 075, 1 035, and 920 cm^{-1}: δ 5.01 (1 H, s), 3.87 (2 H, dd), 1.19 (6 H, s), and 1.09 (3 H, s) (Found: C, 74.8; H, 10.6. Calc. for $C_7H_{12}O$: C, 75.0; H, 10.7%). The latter was (12), yield 10%; $\nu_{max.}$ 3 025, 2 995, 1 695, 1 480, 1 375, 1 345, 1 250, 1 195, 1 130, 1 065, 1 035, 980, 940, and 915 cm^{-1}: δ_H 5.02 (1 H, t), 3.91 (2 H, m), 1.61 (2 H, m), 1.21 (6 H, s), 1.16 (3 H, s); δ_C (p.p.m. downfield from $SiMe_4$) 101.7, 115.9, 82.19, 77.49, 32.52, 31.49, 26.23, and 25.98 (Found: C, 76.0; H, 10.9. Calc. for $C_8H_{14}O$: C, 76.2; H, 11.1%). Compound (8) (2 g) was then reacted with ethyl diazoacetate[12] in the presence of copper acetylacetonate[13] to yield compound (9), yield 54%, b.p. 85—91 °C/0.3 mmHg; $\nu_{max.}$ 3 015, 1 760, 1 620, 1 450, 1 380, 1 315, 1 160, and 1 040 cm^{-1}: δ 4.20 (2 H, dd), 4.19 (2 H, q), 1.30 (3 H, s), 1.28 (3 H, s), 1.14 (3 H, t), 1.10 (3 H, s), and 0.9 to 1.4 (2 H, dd) (Found: C, 66.7; H, 9.1. $C_{11}H_{18}O_3$ requires C, 66.7; H, 9.1%). This was reduced[14] with $NaAlH_4$ in THF at −45 °C: use of the stoicheiometric amount of the reducing agent yielded mainly the aldehyde (10), yield 58%; $\nu_{max.}$ 3 000, 1 740, 1 660, 1 485, 1 380, 1 353, 1 320, 1 275, 1 230, 1 195, 1 075, and 1 045 cm^{-1}: δ 9.43 (1 H, d), 3.42 (2 H, dd), 1.30 (3 H, s), 1.21 (6 H, s), and 0.93—1.28 (2 H, m) (Found: C, 69.9; H, 9.05. $C_9H_{14}O$ requires C, 70.1; H, 9.09%). Use of an excess of reductant resulted in accompanying formation (up to 50%) of the acid (13); $\nu_{max.}$ 3 550, 3 000, 1 758, 1 660, 1 470, 1 395, 1 380, 1 350, 1 320, 1 180, and 1 070 cm^{-1}; δ 12.32 (1 H, s), 3.45 (2 H, m), 2.31 (2 H, m), 1.32 (3 H, d), 1.20 (6 H, s), and 1.15—1.23 (2 H, m): *m/e* 170 (M^+, 12%), 169 (8), 155 (23), 130 (33), 125 (62), 120 (12), 112 (42), 109 (10), 66 (38), 60 (35), 45 (100), 43 (88), and 41 (56). The aldehyde and acid could be separated on a column (15 × 0.5 cm) of silica gel 60 (t.l.c. grade) with CH_2Cl_2. The final step involved addition to (10) (76 mg) of a Wittig reagent prepared from methyltriphenylphosphonium bromide and the conjugate base of DMSO.[15-17] After 3 d at 20 °C, the product was worked up to give an oil (20 mg, 27%), b.p. 89—89.5 °C/3 mmHg that was shown to comprise, using a variety of analytical g.l.c. and t.l.c. systems (see above), two components (36 : 64 v/v). The unresolved mixture had $\nu_{max.}$ 3 000, 1 640, 1 485, 1 380, 1 190, 1 050, 889, and 790 cm^{-1}: δ [assignment, see structure (11)] 1.21 (10 H, s, gfd), 1.61 (1 H, dd, c), 3.69 (2 H, dd, e), 4.98 (2 H, m, a), and 5.58 (1 H, quintet, b): *m/e* 152 (M^+, 25%), 137 (17), 109 (11), 95 (52), 79 (52), 67 (40), 55 (29), and 43 (100) (Found: C, 78.8; H, 10.5. $C_{10}H_{16}O$ requires C, 78.9; H, 10.5%). The components of the mixture could not be separated on a preparative scale using a variety of g.l.c., t.l.c., and h.p.l.c. systems, but comparison of the synthetic product with an authentic sample of artemiseole from *A. tridentata* showed that the minor component was identical in behaviour with the natural product; the other component was presumably its epimer (see text).

Chrysanthemum Lactone.—Compound (12) (0.5 g), obtained as above was oxidised,[18] with a stoicheiometric amount of SeO_2 (0.44 g) in dioxan (10 ml) and H_2O (1 ml) for 36 h at reflux to yield (14) (0.39 g, 71%); $\nu_{max.}$ 3 450, 3 000, 1 720, and 1 550 cm^{-1}; δ 1.10 (6 H, s), 1.62 (3 H, s), 2.20 (2 H, d), 4.10 (1 H, s), 5.60 (1 H, m), and 11.53 (1 H, s). Compound (14) was further oxidised under the same conditions with a further 1 equiv. of SeO_2 to yield (15) (0.27 g, 78%); $\nu_{max.}$ 3 400, 3 000, 1 740, and 1 680 cm^{-1}: δ 1.21 (6 H, s), 2.32 (3 H, s), 5.21 (1 H, s), 6.33 (1 H, s), and 12.52 (1 H, s). Compound (15) (0.23 g) was then submitted to a Wittig reaction[15-17] with the ylide prepared from ethyltriphenylphosphonium bromide and the conjugate base of DMSO to yield compound (16) (0.162 g, 70%); $\nu_{max.}$ 3 400, 1 950, 1 740, and 1 680 cm^{-1}: δ 1.45 (6 H, s), 1.78 (3 H, s), 1.88 (3 H, s), 4.49 (1 H, s), 5.27 (1 H, s), and 6,42 (1 H, m). Compound (16),

(0.16 g), was then lactonised by stirring with 2,2′-dipyridyl disulphide (0.29 g) and triphenylphosphine (0.35 g) in xylene (25 ml) under N_2 at 20 °C for 16 h; [19-21] the mixture was then diluted with O_2-free xylene (50 ml) and the resultant solution was added over 48 h to dry xylene (250 ml) at reflux under N_2, and stirring was continued for a further 48 h after removal of the solvent under reduced pressure. The product was chromatographed on a column (15 × 0.5 cm) of silica gel (type 60; t.l.c. grade) with Et_2O–pentane (1 : 9 v/v) to yield compound (17) (93 mg, 60%); $\nu_{max.}$ 2 980, 1 725, 1 690, 1 460, 1 380, 1 350, 1 320, 1 230, 1 205, 1 115, and 1 095 cm^{-1}: δ 1.59 (6 H, s), 1.92 (3 H, s), 2.01 (3 H, d), 5.85 (1 H, q), and 6.89 (1 H, s); *m/e* 166 (M^+, 25%), 153 (32), 151 (100), 138 (15), 123 (23), 110 (13), 108 (9), and 55 (30) (Found: C, 72.2; H, 8.5. Calc. for $C_{10}H_{14}O_2$: C, 72.2; H, 8.4%). On addition of $Eu(fod)_3$, shifts (Δδ) from the unperturbed spectrum were found as follows [reagent/substrate = 1.0; assignment, see structure (17)]: H_c 8.30, H_b 5.09, H_a 5.31, H_d 1.10, H_e 5.12, and H_f 2.80. The *E*-isomer (17), 30 mg, was converted into its equilibrium mixture with the *Z*-compound by photolysis in C_6H_6 (20 ml) using a mercury lamp (Mazda; 90 W) for 3 d. After this period, g.l.c. analysis (Carbowax 20 M; 6 m × 0.3 cm; 150 °C) indicated a mixture of (17) and (18) (30 : 70 w/v).

We thank the University of London for a studentship (to P. N. C.).

[9/1651 *Received*, 17*th October*, 1979]

REFERENCES

[1] E. H. Hoegger, *Proc. Mont. Acad. Sci.*, 1973, **33**, 97 (*Chem. Abs.*, 1974, **81**, 49852).
[2] H. Buttkus and R. Bose, *J. Amer. Oil Chemists Soc.*, 1977, **54**, 212.
[3] D. V. Banthorpe and P. N. Christou, *Phytochemistry*, 1979, **18**, 666.
[4] T. A. Noble and W. W. Epstein, *Tetrahedron Letters*, 1977, 3931.
[5] F. Bohlmann and G. Florenz, *Chem. Ber.*, 1966, **99**, 990.
[6] F. Bohlmann and M. Grenz, *Tetrahedron Letters*, 1969, 2413.
[7] S. Yamagiwa, H. Noswegi, and H. Uda, *Bull. Chem. Soc. Japan*, 1978, **51**, 3011.
[8] R. A. Walsh and A. T. Bottini, *J. Org. Chem.*, 1970, **35**, 1086.
[9] S. Patai, ' The Chemistry of the Ether Linkage,' Wiley, London, 1967, p. 46.
[10] D. V. Banthorpe, D. Baxendale, G. Gatford, and S. R. Williams, *Planta med.*, 1971, **20**, 147.
[11] F. L. Greenwood, M. D. Kellert, and J. Sedlan, *Org. Synth.*, Coll. Vol. IV., 1963, 108.
[12] X. Creary, *J. Org. Chem.*, 1978, **43**, 1777.
[13] M. M. Jones, *J. Amer. Chem. Soc.*, 1959, **81**, 3188.
[14] L. I. Zakharkin, V. V. Gavrilenko, D. N. Maslin, and I. M. Khorlina, *Tetrahedron Letters*, 1963, 2087.
[15] R. Greenwald, M. Chaykovski, and E. J. Corey, *J. Org. Chem.*, 1963, **28**, 1128.
[16] G. Wittig and K. Schoellkopf, *Org. Synth.*, 1960, **40**, 66.
[17] E. J. Corey and M. Chaykovski, *J. Amer. Chem. Soc.*, 1962, **84**, 866.
[18] K. B. Wiberg and S. D. Nielsen, *J. Org. Chem.*, 1964, **29**, 3353.
[19] E. J. Corey and M. C. Nicolaou, *J. Amer. Chem. Soc.*, 1974, **96**, 5614.
[20] W. Marckwald, *Ber.*, 1900, **33**, 1556.
[21] G. Brauer, ' Handbook of Preparative Inorganic Chemistry,' Academic Press, New York, 2nd edn., 1963, vol. I, p. 294.