Tetrahedron Letters, Vol.31, No.17, pp 2393-2396, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

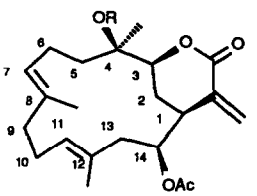
TOTAL SYNTHESIS OF (±)-CRASSIN ACETATE METHYL ETHER

William G. Dauben,* Ting-zhong Wang and Randall W. Stephens

Department of Chemistry, University of California, Berkeley, CA 94720

Abstract: The total synthesis of (±)-crassin acetate methyl ether consists of two major operations, macrocyclization and lactone ring formation. The basic stereochemical control unit was 5β-benzyloxynorbornan-2-one.

Since the first structure proof some 25 years ago,[1] cembranoids have become one of the most widely occurring families of diterpenes in nature. Many cembranoids isolated from the gorgonians and soft corals which feature an α-methylene lactone moiety are referred to as cembranolides. One of the first cembranolides isolated in 1962 from Caribbean gorgonian *pseudoplexaura porosa* was crassin acetate **1**[2] which has a wide range of biological



1, R=H

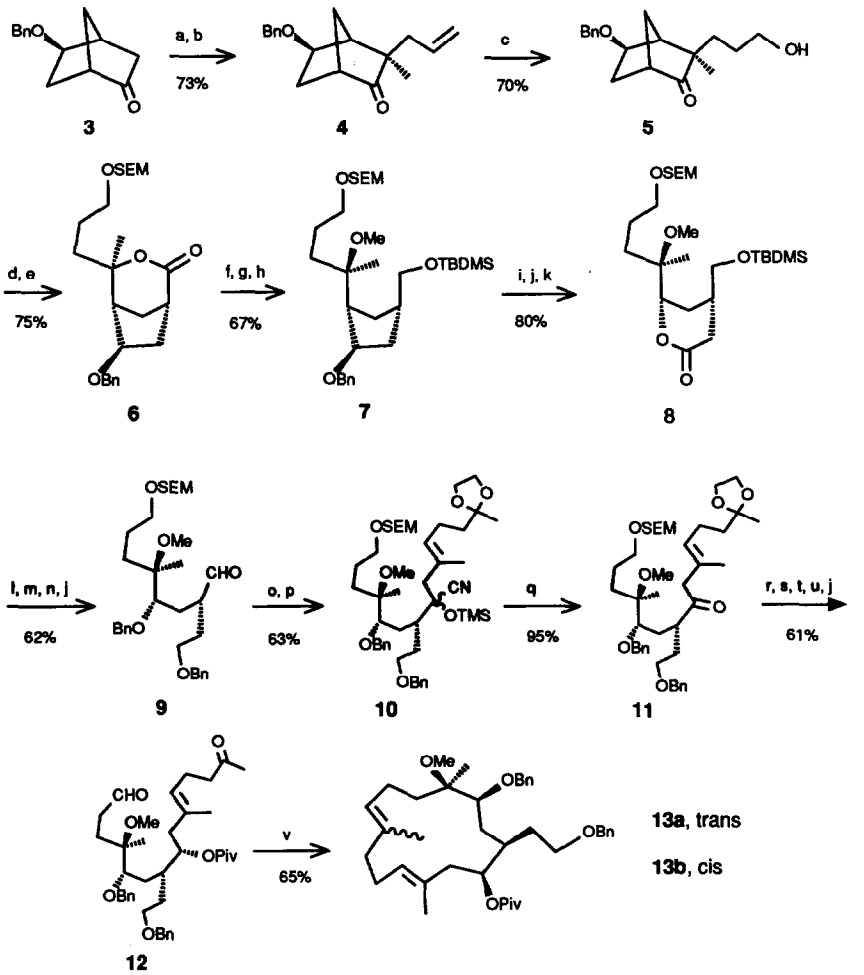
2, R=CH_3

activities. Since its structure was elucidated by chemical methods and its absolute configuration was established by X-ray diffraction studies,[3] it has been a challenging target for synthetic organic chemists, and only very recently, a synthesis of crassin alcohol was reported.[4] Here we report a total synthesis of crassin acetate methyl ether **2**.

The synthesis consists of two major operations, macrocyclization and lactone ring formation. The macrocyclization relies on a McMurry coupling for the formation of the $C_{7,8}$ double bond while the reactivity of the α-methylene lactone moiety in **2** necessitates its introduction at the end of the synthesis. To control the stereochemistry at C_1, C_3, and C_4, rigid benzyloxynorbornone **3**[5] was chosen as the building block. As shown in Scheme 1, methylation of **3**, followed by allylation with LDA and allyl bromide gave fully substituted ketone **4** as a single diastereomer in good yield.[6] Alcohol **5** was formed in 70% overall yield by a ketalization, hydroboration,

deketalization sequence. Baeyer-Villiger oxidation of ketone **5** with peracetic acid delivered regiospecifically one lactone.[7] The hydroxy group was protected as trimethysilylethoxymethyl ether,[8] and the lactone **6** was reduced to

Scheme 1

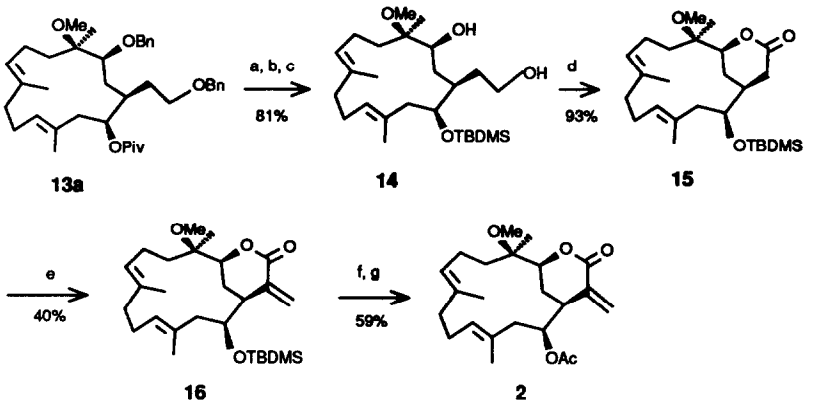


Reagents: (a) LDA, MeI; (b) LDA, allyl bromide; (c)1, ethylene glycol, TsOH; 2, BH_3-THF, -78 °C to rt.; H_2O_2, OH^-; 3, H_3O^+; (d) CH_3CO_3H, Na_2HPO_4, $CHCl_3$; (e) SEMCl, $(i\text{-}Pr)_2NEt$; (f) LAH, 0 °C; (g) t-BuMe$_2$SiCl, imidazole, DMF; (h) NaH, MeI, DMF; (i) H_2, 10% Pd/C, EtOAc; (j) Swern oxidation; (k) m-CPBA, Na_2HPO_4, CH_2Cl_2; (l) LAH, 0 °C to rt; (m) NaH, BnBr, $(n\text{-}Bu)_4NI$, DMF; (n) AcOH-H_2O-THF (3:1:1), 55 °C; (o) Me_3SiCN, 18-crown-6, KCN; (p) LDA, (E)-2-(4-bromomethyl-3-pentenyl)-2-methyl-1,3-dioxolane; (q) $(n\text{-}Bu)_4NF$, THF; (r) LAH, -78 °C to rt; (s) PivCl, Et_3N, THF, reflux; (t) $(n\text{-}Bu)_4NF$, HMPA, 105 °C; (u) 5% HCl, THF; (v) $TiCl_3$, Zn-Cu, DME, reflux.

a diol. The primary hydroxy group was protected as a t-butyldimethylsilyl ether, and the hindered tertiary alcohol

was then converted to methyl ether **7**. The fully protected compound **7** was debenzylated and the resulting alcohol was oxidized to a ketone by the Swern method. Again, Baeyer-Villiger oxidation of the ketone afforded the desired lactone **8** as a single isomer. The lactone was reduced with LAH and the resulting diol was protected as a dibenzyl ether. The t-butyldimethylsilyl ether was cleaved and the resulting alcohol was oxidized to labile aldehyde **9**. Addition of the allylic anion generated from (E)-2-methyl-2-(4-methyl-5-phenylthio-3-pentenyl)-1,3-dioxolane with lithium naphthalenide to aldehyde under a variety of conditions[9] gave exclusively one product with an isomerized cis-$C_{11,12}$ double bond. In order to obtain a trans configuration of the double bond, some kind of *umpolung* synthon of the aldehyde carbonyl had to be considered. To this end, the aldehyde was transformed to the cyanohydrin trimethylsilyl ether which was deprotonated and alkylated with the corresponding trans allylic bromide to give cyanohydrin derivative **10**.[10] Exposure of **10** to TBAF in THF for 10 min (prolonged reaction time causes epimerization of the α-carbon) gave ketone **11**. This labile ketone was immediately reduced with LAH to give a 1:1 mixture of isomeric alcohols; each isomer was carried through the following synthesis starting with conversion to pivalates. Keto aldehyde **12** was macrocyclized with $TiCl_3$/Zn-Cu[11] in refluxing DME to give a mixture (t:c = 4:3, 65%) of two isomers **13a** and **13b** which were separable by chromatography on silica gel (3% ethyl acetate/ petroleum ether). This reaction demonstrated that McMurry coupling methodology could be applied to highly oxygenated substrates, widening the scope of this method. Assignment of the $C_{7,8}$ double bond stereochemistry in **13** was made possible by the fact that ^{13}C NMR chemical shifts of methyl groups at trisubstituted olefins differ by about 10 ppm (trans, 13-19 ppm; cis, 22-29 ppm).[12]

Scheme 2



Reagents:(a) LAH, 0 °C; (b) t-BuMe_2SiCl, imidazole, DMF, 70 °C; (c) Li, NH_3; (d) Ag_2CO_3/Celite, benzene; (e)1, LDA, CH_2=NMe_2I; 2, MeI, MeOH; 3, DBU, THF; (f)1, (n-Bu)$_4$NF, THF; 2, 5% HCl; (g) Ac_2O, DMAP, CH_2Cl_2.

With the 14-membered ring closed, the remaining task was to construct the lactone ring (Scheme 2). Thus, trans isomer **13a** was converted to diol **14** in three steps. The diol was oxidized to the desired lactone with silver carbonate on Celite[13] (Fetizon reagent) in excellent yield. Introduction of the α-methylene group was accomplished with Eschenmoser's salt.[14] Desilylation of **16**, followed by acetylation, gave the title compound which was identical in all respects to the sample prepared by methylation of natural crassin acetate.

Using the same methodology, cis isomer **13b** has been transformed to the isomer of the titled compound and both isomers will be evaluated for their biological activities.

Acknowledgement: This research was supported by Grant No. GM 27320, National Institute of General Medical Sciences, U.S. Public Health Service.

References

1. Dauben, W. G.; Thiessen, W. E.; Resnick, P. R. *J. Am. Chem. Soc.* **1962**, *84*, 2015.
2. Weinheimer, A. J.; Ciereszko, L. S.; Eufford, D. S. *Annul. Rev. N. Y. Acad. Sci.* **1960**, *90*, 917.
3. Hossain, M. B.; van der Helm, D. *Recl. Trav. Chim. Pay-Bas* **1969**, *88*, 1413.
4. McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 8928.
5. Meinwald, J.; Crandall, J. K. *J. Am. Chem. Soc.* **1966**, *88*, 1292.
6. For *exo* selectivity of alkylation on norbornyl ketones, see: Corey, E. J.; Vatakencherry, P. A. *J. Am. Chem. Soc.* **1962**, *84*, 2611.
7. Meinwald, J.; Frauenglass, E. *J. Am. Chem. Soc.* **1960**, *82*, 5235.
8. Lipshultz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.
9. (a) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713; (b) Cohen, T.; Guo, B.; Doubleday, W. *J. Am. Chem. Soc.* **1987**, *109*, 4710.
10. (a) Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, 4929; (b) Hertenstein, U.; Hunig, S.; Oller, M. *Synthesis* **1976**, 416.
11. McMurry, J. E.; Kees, K. L. *J. Org. Chem.* **1977**, *42*, 2655.
12. (a) Martin, G. E.; Matson, J. A.; Turley, J. C.; Weinheimer, A. J. *J. Am. Chem. Soc.* **1979**, *101*, 1888; (b) Kashman, Y.; Carmely, S.; Groweiss, A. *J. Org. Chem.* **1981**, *46*, 3592.
13. Fetizon, M.; Golfier, M.; Louis, J-M. *Tetrahedron* **1975**, *31*, 171.
14. Roberts, J. L.; Borromeo, P. S.; Poulter, C. D. *Tetrahedron Lett.* **1977**, 1621.

(Received in USA 16 February 1990)