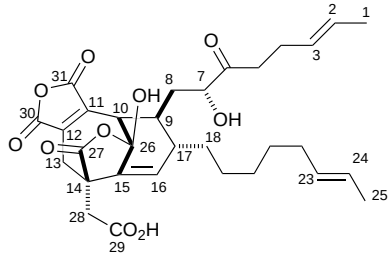
Synthesis of the carbobicyclic substructure of CP-225,917 and CP-263,114

Paulo W. M. Sgarbi and Derrick L. J. Clive*

Chemistry Department, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

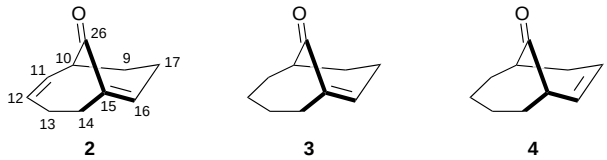
The bridgehead alkenic ketones 22a and 22b, representing the carbobicyclic substructure of the squalene synthase and farnesyl transferase inhibitors CP-225,917 (1) and CP-263,114 (23), have been synthesized from the 7-norbornenone acetal 8, using an anionic oxy-Cope rearrangement of 21a and 21b in the key step; the synthesis serves as a test of a potential route to both natural products.

The structurally complex anhydride **1** was isolated from the fermentation broth of an unidentified fungus, and described recently by chemists at Pfizer Central Research.[1,2] The substance is related to the nonadrides[3]—at least on the basis of its proposed[2] biosynthetic origin. It was given the designation CP-225,917, and was found[1] to inhibit squalene synthase[4] (from rat liver) and Ras farnesyl transferase[5] (from rat brain). Inhibition of these enzymes represents an opportunity for controlling serum cholesterol levels[6] as well as certain types of abnormal cell growth,[5] and so **1** may serve as a lead in the design of cholesterol-lowering and anticancer drugs.



1

CP-225,917 is the hemiacetal of a bicyclo[4.3.1]decadienone substructure **2**,† and one of its notable features is the bridgehead double bond. Although the related olefinic ketone **3** (which was obtained in admixture with the isomer **4**) has been prepared,[7] the method used to make that particular compound does not seem well-suited to the task of synthesizing the natural product. We report a model study[8,9] that establishes a route to **22a** and **22b** (see Scheme 2), both of which we take to represent the [4.3.1]-carbobicyclic substructure of CP-225,917.

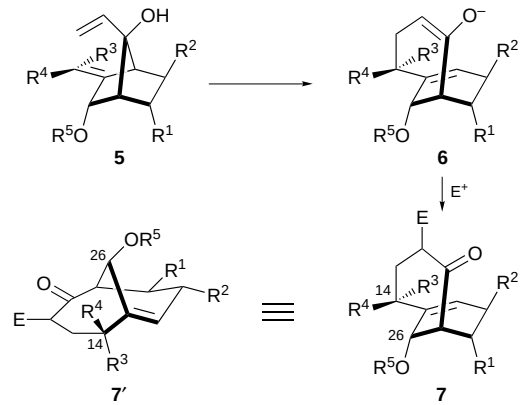


2 **3** **4**

Our approach is based on the idea that anionic oxy-Cope rearrangement‡ of compounds such as **5** (Scheme 1) should lead to enolates **6**, which have a number of features that are appropriate for further elaboration in the desired manner (**6**→**7**/**7′**). In particular, the C(26) oxygen function of **7**/**7′** could provide the corresponding acetal unit of **1**, and the enolate **6** would offer several opportunities for constructing the anhydride, perhaps by initial capture with an electrophile, such as Mander's reagent.[11] The route summarized in Scheme 1 should also be able to accommodate introduction of two substituents at C(14) (see **7**/**7′**), which is a quaternary centre in the natural product.

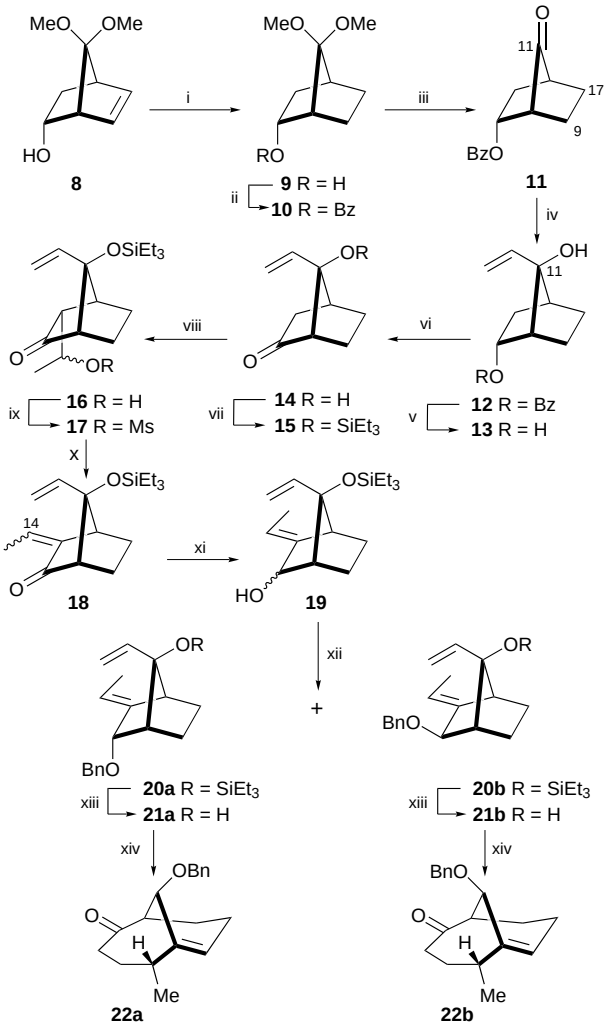
Our model study (Scheme 2) began with the readily available norbornene **8**.[12] The double bond was first saturated (**8**→**9**; Pd–C, H_2; 92%), and the resulting alcohol was then benzoylated (BzCl, pyridine; 98%) and treated with aqueous acetic acid to hydrolyse the acetal (**9**→**10**→**11**). When esterification was omitted, extensive decomposition occurred during attempts at deacetalization, presumably by a retroaldol process. Ketone **11** is quite sensitive, and so it was used without purification. While we had originally planned to introduce a vinyl group at C(11) (*cf.* **11**→**12**) by an intramolecular Barbier reaction, we wondered if adequate facial selectivity would be observed for a simple intermolecular process[13] and, in the event, treatment of crude **11** with vinylmagnesium bromide in Et_2O gave a ≥5 : 1 mixture of tertiary alcohols, with the desired isomer **12** being the major product. In the present study, carbons C(9) and C(17) of **11** are unsubstituted; in a more advanced model those carbons would carry alkyl groups, and steric factors may improve the already satisfactory product ratio. Separation of the C(11) isomers could be performed chromatographically after hydrolysis of the benzoyl group (**12**→**13**; LiOH, 9 : 1 THF–water, 60 °C; 44% overall from **10**; 9% of C(11) isomer of **13**). Oxidation of the major diol (**13**) was initially problematic, until we tried the Dess–Martin reagent,[14] which smoothly converts **13** into keto alcohol **14** (93%).

The next task was to protect the tertiary hydroxy group (**14**→**15**) in order to avoid retroaldol fragmentation.[15] Et_3-SiOTf in the presence of 2,6-lutidine proved to be a satisfactory combination of reagents (84%); attempts to introduce *tert*-butyldimethylsilyl or *p*-methoxybenzyl groups were unsuccessful. The remainder of the hexa-1,5-diene subunit required for the anionic oxy-Cope rearrangement was assembled by a short sequence, beginning with aldol condensation (**15**→**16**; LDA, THF, −78 °C; excess of MeCHO; > 76%), so as to form the β-hydroxy ketones **16** as an isomer mixture. Without separation, these alcohols were converted into the corresponding mesylates **17** (MsCl, Et_3N, CH_2Cl_2, 0 °C) and, again without isomer separation, the mesylates were treated with DBU (THF, room temperature), affording the desired enones **18**, which were easily separable (*E*-isomer, 60% overall from **15**; *Z*-isomer, 11% overall from **15**).§ As a matter of convenience, only the major ketone was taken further. Reduction (**18**→**19**; $NaBH_4$,



5 **6** **7′** **7**

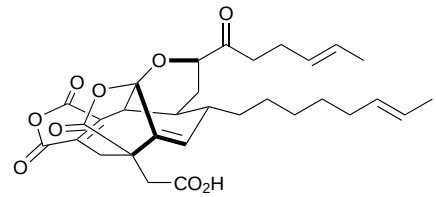
Scheme 1



Scheme 2 *Reagents and conditions*: i, H_2, 10% Pd–C, MeOH, room temp., *ca*. 5 h, 92%; ii, BzCl, pyridine, room temp., 10 h, 98%; iii, 6 : 1 AcOH–H_2O, 150 °C, 40 min; iv, H_2C=CHMgBr, Et_2O, 0 °C, 40 min; v, LiOH·H_2O, 9 : 1 THF–H_2O, 80 °C, 12 h, 53% over 3 steps [44% for **13**, 9% for C(11) isomer of **13**]; vi, Dess–Martin periodinane, 33 : 1 CH_2Cl_2–DMSO, room temp., 12 h, 93%; vii, $Et_3SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, room temp., 1 h, 84%; viii, LDA, THF, −78 °C, 1 h, then MeCHO, −78 °C, 1 h; ix, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C; x, DBU, THF, room temp., 1 h, 71% over 3 steps [60% isolated yield of (*E*)-alkene and 11% isolated yield of (*Z*)-alkene]; xi, $NaBH_4$, $CeCl_3$·$7H_2O$, MeOH, room temp., 1.5 h, 86% (*endo*-**19**, 42%; *exo*-**19**, 44%); xii, BnBr, NaH, THF, 70 °C, 24 h, 94% for **20a**, 70% for **20b**; xiii, Bu_4NF, THF, room temp., 2 min, 89% for **21a**, 89% for **21b**; xiv, $(Me_3Si)_2NK$, PhMe, 100 °C, 20 h, 95% for **22a**, 82% for **22b**

MeOH, $CeCl_3$·$7H_2O$; 86%) gave a 1 : 1 mixture of *endo*- (42% isolated yield) and *exo*-alcohols (44%), which were easily separated and individually protected by benzylation (*endo*-**19**→**20a**, 94%; *exo*-**19**→**20b**, 70%). At this point, desilylation of both **20a** and **20b** was accomplished under standard conditions (Bu_4NF, THF, room temperature; 89% for each compound) and finally, the resulting alcohols were subjected to anionic oxy-Cope rearrangement [$(Me_3Si)_2NK$, PhMe, 100 °C, *ca*. 20 h]. *endo*-Benzyl ether **21a** gave the bridgehead keto alkene **22a** (95%) and the *exo* isomer (**21b**) gave **22b** (82%), whose structures were confirmed by extensive ^1H–^1H COSY and ROESY NMR measurements. In neither case was the rate of oxy-Cope rearrangement noticeably increased by addition of 18-crown-6.

Formation of **22a** and **22b** (which is crystalline) serves as an initial test of the plan summarized in Scheme 1.



23

A closely related natural product (CP-263,114, **23**) was isolated along with CP-225,917, and found to have similar biological properties, although of a lower potency with respect to squalene synthase inhibition. The present work is, of course, equally relevant to the synthesis of the congener.

All new compounds, except **11**, one epimer of **16**, **17** and the C(11) epimer of **12**, were satisfactorily characterized by spectroscopic methods, including high resolution mass spectroscopic measurements.

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Footnotes and References

* E-mail: derrick.clive@ualberta.ca

† We use the non-systematic numbering given in ref. 2.

‡ For recent examples of the preparation of bicyclic systems by anionic oxy-Cope rearrangement, see ref. 10.

§ We have not yet explored the possibility of conjugate addition for introducing what will eventually be the second substituent at the quaternary centre [C(14)].

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