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

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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 nonadrides³—at least on the basis of its proposed² biosynthetic origin. It was given the designation CP-225,917, and was found¹ to inhibit squalene synthase⁴ (from rat liver) and Ras farnesyl transferase⁵ (from rat brain). Inhibition of these enzymes represents an opportunity for controlling serum cholesterol levels⁶ 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.



CP-225,917 is the hemiacetal of a bicyclo[4.3.1]decadienone substructure $2,\dagger$ 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.



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 $(6 \rightarrow 7/7')$. 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 ($8 \rightarrow 9$; 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 $(9 \rightarrow 10 \rightarrow 11)$. 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. $11 \rightarrow 12$) by an intramolecular Barbier reaction, we wondered if adequate facial selectivity would be observed for a simple intermolecular process13 and, in the event, treatment of crude 11 with vinylmagnesium bromide in Et₂O gave a $\geq 5:1$ 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 $(12 \rightarrow 13; \text{LiOH}, 9:1 \text{ THF})$ 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 $(14\rightarrow 15)$ in order to avoid retroaldol fragmentation.¹⁵ Et₃-SiOTf in the presence of 2,6-lutidine proved to be a satisfactory combination of reagents (84%); attempts to introduce tertbutyldimethylsilyl 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 ($15 \rightarrow 16$; 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, Et₃N, CH₂Cl₂, 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 \rightarrow 19; NaBH₄,



Chem. Commun., 1997 2157



Scheme 2 Reagents and conditions: i, H₂, 10% Pd–C, MeOH, room temp., ca. 5 h, 92%; ii, BzCl, pyridine, room temp., 10 h, 98%; iii, 6:1 AcOH– H₂O, 150 °C, 40 min; iv, H₂C=CHMgBr, Et₂O, 0 °C, 40 min; v, LiOH·H₂O, 9:1 THF–H₂O, 80 °C, 12 h, 53% over 3 steps [44% for **13**, 9% for C(11) isomer of **13**]; vi, Dess–Martin periodinane, 33:1 CH₂Cl₂–DMSO, room temp., 12 h, 93%; vii, Et₃SiOSO₂CF₃, 2,6-lutidine, CH₂Cl₂, room temp., 1 h, 84%; viii, LDA, THF, -78 °C, 1 h, then MeCHO, -78 °C, 1 h; ix, MeSO₂Cl, Et₃N, CH₂Cl₂, 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, NaBH₄, CeCl₃·7H₂O, 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, Bu₄NF, THF, room temp., 2 min, 89% for **21a**, 89% for **21b**; xiv, (Me₃Si)₂NK, PhMe, 100 °C, 20 h, 95% for **22a**, 82% for **22b**

MeOH, CeCl₃·7H₂O; 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 \rightarrow 20a, 94%; *exo*-19 \rightarrow 20b, 70%). At this point, desilylation of both 20a and 20b was accomplished under standard conditions (Bu₄NF, THF, room temperature; 89% for each compound) and finally, the resulting alcohols were subjected to anionic oxy-Cope rearrangement [(Me₃Si)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.



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.

Acknowledgment is made to the Natural Sciences and Engineering Research Council of Canada for financial support, and we thank Dr Yunxin Bo for advice. P. W. M. S. held a Graduate Scholarship from CNPq (Brazil).

Footnotes and References

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† 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)].

- 1 T. T. Dabrah, H. J. Harwood, L. H. Huang, N. D. Jankovich, T. Kaneko, J.-C. Li, S. Lindsey, P. M. Moshier, T. A. Subashi, M. Therrien and P. C. Watts, J. Antibiot., 1997, 50, 1.
- 2 T. T. Dabrah, T. Kaneko, W. Massefski, Jr. and E. B. Whipple, J. Am. Chem. Soc., 1997, 119, 1594.
- 3 E.g. J. E. Baldwin, D. H. R. Barton and J. K. Sutherland, J. Chem. Soc., 1965, 1787 and earlier papers in the series; J. K. Sutherland, Fortschr. Chem. Org. Naturst., 1967, 25, 131.
- 4 N. S. Watson and P. A. Procopiou, *Prog. Med. Chem.*, 1996, **33**, 331. 5 S. B. Singh, J. M. Liesch, R. B. Lingham, M. A. Goetz and J. B. Gibbs,
- J. Am. Chem. Soc., 1994, **116**, 11 606 and references cited therein.
- 6 J. D. Bergstrom, M. M. Kurtz, D. J. Rew, A. M. Amend, J. D. Karkas, R. G. Bostedor, V. S. Bansal, C. Dufresne, F. L. VanMiddlesworth, O. D. Hensens, J. M. Liesch, D. L. Zink, K. E. Wilson, J. Onishi, J. A. Milligan, G. Bills, L. Kaplan, M. Nallin Omstead, R. G. Jenkins, L. Huang, M. S. Meinz, L. Quinn, R. W. Burg, Y. L. Kong, S. Mochales, M. Mojena, I. Martin, F. Pelaez, M. T. Diez and A. W. Alberts, *Proc. Natl. Acad. Sci. USA*, 1993, **90**, 80; J. L. Goldstein and M. S. Brown, *Nature*, 1990, **343**, 425.
- 7 B. G. Cordiner, M. R. Vegar and R. J. Wells, *Tetrahedron Lett.*, 1970, 2285; cf. H. O. House and T. V. Lee, J. Org. Chem., 1979, 44, 2819.
- 8 Cf. K. C. Nicolaou, M. W. Härter, L. Boulton and B. Jandeleit, Angew. Chem., Int. Ed. Engl., 1997, 36, 1194.
- 9 Cf. H. M. L. Davies, R. Calvo and G. Ahmed, Tetrahedron Lett., 1997, 38, 1737.
- 10 S. F. Martin, J.-M. Assercq, R. E. Austin, A. P. Dantanarayana, J. R. Fishpaugh, C. Gluchowski, D. E. Guinn, M. Hartmann, T. Tanaka, R. Wagner and J. B. White, *Tetrahedron*, 1995, **51**, 3455; L. A. Paquette, *Chem. Soc. Rev.*, 1995, **24**, 9.
- 11 L. N. Mander and S. P. Sethi, Tetrahedron Lett., 1983, 24, 5425.
- 12 L. A. Paquette, K. S. Learn, J. L. Romine and H.-S. Lin, J. Am. Chem. Soc., 1988, 110, 879.
- 13 Cf. G. Mehta and F. Ahmad Khan, J. Am. Chem. Soc., 1990, **112**, 6140; G. Mehta, F. Ahmad Khan, B. Ganguly and J. Chandrasekhar, J. Chem. Soc., Perkin Trans. 2, 1994, 2275.
- 14 R. E. Ireland and L. Liu, J. Org. Chem., 1993, 58, 2899.
- 15 Cf. L. A. Paquette and M.-A. Poupart, J. Org. Chem., 1993, 58, 4245.

Received in Corvallis, OR, USA, 18th August 1997; 7/06075K