Pergamon

Tetrahedron Letters 40 (1999) 4605–4609

TETRAHEDRON LETTERS

Synthesis of tricyclic bridgehead olefins related to the core structure of CP-225,917 and CP-263,114 — solvent, strain, and substitution effects on siloxy-Cope rearrangements

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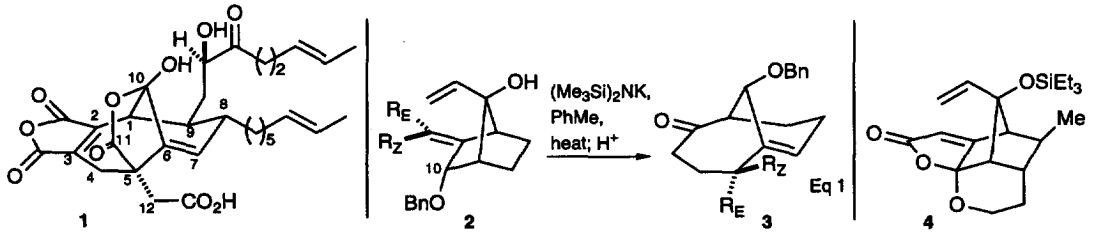
Received 5 February 1999; accepted 26 March 1999

Abstract

Siloxy-Cope rearrangements have been used to make bridgehead olefins, such as **15**, **16b**, **23b** and **36** — all related to the core of CP-225,917 and CP-263,114.

In an earlier communication[1] we described a strategy (cf. Eqn. 1), based on anionic oxy-Cope rearrangement, for converting [2.2.1] bicyclic compounds[2] into substances that resemble the core structure of the Ras farnesyl transferase inhibitor CP-225,917 (**1**)[3,4] and the closely-related CP-263,114.[3] The plan was illustrated for the particular case of **2** (R_E=Me, R_Z=H, Eqn. 1) and its 10-*exo* isomer.



1 **2** **3** **4**

This approach[5] has been studied by Bio and Leighton, who recently described[6] a milder version of the oxy-Cope process, that owes its facility — for reasons indicated below — to at least one of the additional rings (see **4**) incorporated into the starting material. We report our own findings in connection with the critical rearrangement step (cf. **2** → **3**). Anionic oxy-Cope reaction of **2** (R_E=Me, R_Z=H) required[1] severe conditions [$(Me_3Si)_2NK$, PhMe, 100°C, 20 h], but proceeded in high yield [95%, and 82% for the C(10) epimer]. The rate of reaction was not noticeably increased by addition of 18-crown-6.

We have now studied other compounds related to **2**, and have found that anionic rearrangement does not proceed if the ethylidene unit is modified by increase in chain length (**2**, R_E=CH_2CH_2OPmb[7] or

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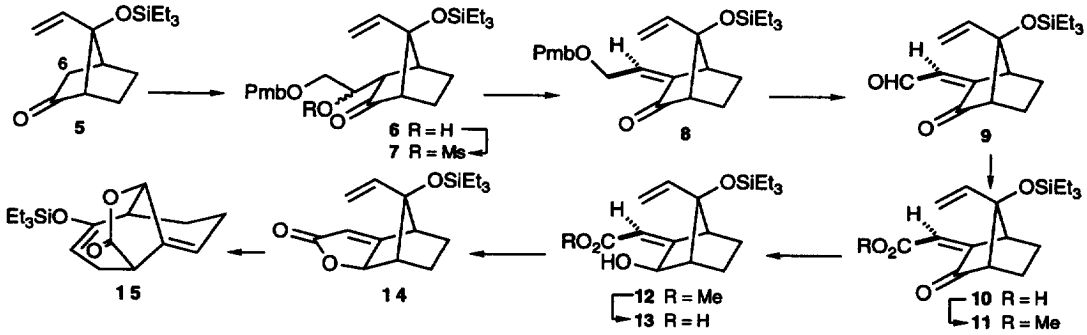
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00743-1

CH_2OBn,[7] R_Z=H). Likewise, we were unable to effect anionic rearrangement of **2** (R_E=R_Z=CH_2OBn),[8] either as the C(10) *exo* or *endo* isomer.

In considering ways of facilitating the rearrangement, we noticed from models that incorporation of one of the double bonds of the 1,5-diene subunit into a lactone ring, as in **14** (Scheme 1), generates in the [2.2.1] bicyclic structure additional strain, which should provide a driving force. Accordingly, **14** was prepared and subjected to thermolysis. Aldol condensation of the readily available[1] ketone **5** with 2-[(4-methoxyphenyl)methoxy]acetaldehyde[9] (**5** → **6**, LDA, THF, −78°C, 1 h; *p*-$MeOC_6H_4CH_2OCH_2CHO$, 3 h; 94%), mesylation (MsCl, Et_3N, CH_2Cl_2, 0°C to rt, 12 h; 97%), and treatment with DBU (THF, rt, 1 h) gave *Z*-olefin **8** (58% yield), as well as the corresponding *E*-isomer (30%). Removal of the (4-methoxyphenyl)methyl group was done in such a way as to lead directly to an aldehyde (**8** → **9**, DDQ, 2.3 equiv., CH_2Cl_2, 12 h; 94%) so that a single further oxidation ($NaClO_2$, NaH_2PO_4, *t*-BuOH, MeCN, 2-methyl-2-butene, H_2O, 0°C, 15 min; 90%) provided acid **10**, which was then esterified (**10** → **11**, CH_2N_2, Et_2O, MeOH; 96%). At this point, reduction ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°C, 2 h) gave largely (65%) the desired *exo* alcohol **12**. We have not attempted to recycle (by oxidation and reduction) the *endo* isomer, which was isolated in 17% yield. Ester hydrolysis (LiOH, THF–H_2O, rt, 4 h; 98%) liberated hydroxy acid **13**, and this could be cyclized to lactone **14** by treatment with 2-chloro-1-methylpyridinium iodide[10] (Et_3N, CH_2Cl_2, reflux, 34 h; 81%). When **14** was heated in refluxing 1,2-dichlorobenzene for 40 min, it was converted cleanly into **15**, isolated in 79% yield. The reaction occurs more easily than other thermal rearrangements we have examined (see below); evidently, the additional strain associated with the lactone unit of **14** facilitates the oxy-Cope process, and it is fortunate that the strain in **14** does not hinder its formation from **13**, or render it very sensitive to hydrolysis.

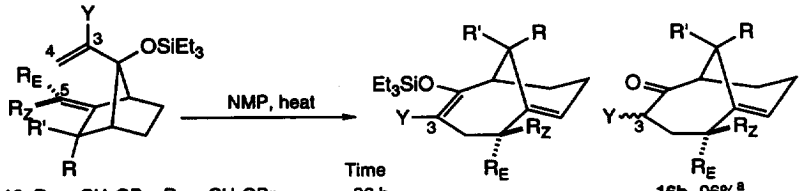


Scheme 1.

While these experiments were in progress, we examined the use (see Table 1) of *N*-methylpyrrolidinone (NMP, bp 204°C), which is known to accelerate oxy-Cope rearrangement of alcohols.[11,12] With alcohol **2** (R_E=R_Z=CH_2OBn), we obtained **16b** (=**3**, R_E=R_Z=CH_2OBn) in 30% yield [corrected for recovered **2** (33%)] after 96 h. We also tried this solvent (96 h) with the corresponding silyl ether **16**, prepared as summarized in Scheme 2, and isolated **16b** in 96% yield [corrected for recovered **16** (50%)] (Table 1). Likewise, compound **17** gave **17b** [24 h, 68%, corrected for recovered **17** (23%)]; in refluxing 1,2-dichlorobenzene (bp 180°C) **17a** was formed slowly [240 h, 86% yield, corrected for recovered **17** (36%)] and, with diphenyl ether (bp 259°C, 14 h), **17b** could be isolated (35%, complete reaction) after aqueous workup.

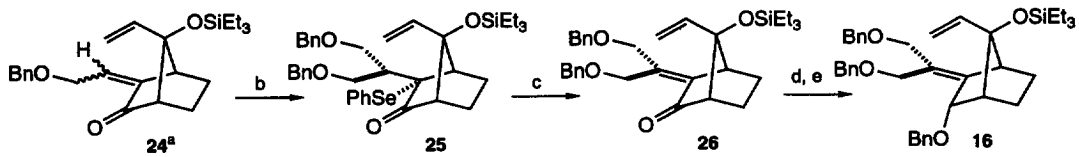
Our experiments suggested that thermolysis of silyl ethers (as opposed to alcohols) in NMP is a satisfactory procedure, and we have found that the reaction works smoothly (Table 1), although we have not established the stage at which desilylation occurs. Reactions are very clean in *degassed* solvent and,

Table 1



		Time		
16	$R_E = CH_2OBn$, $R_Z = CH_2OBn$, R' = H, R = OBn, Y = H	96 h	-	**16b** 96%[a]
17	$R_E = CH_2OBn$, $R_Z = H$, R' = H, R = OBn, Y = H	24 h	**17a** -	**17b** 68%[b]
18	$R_E = CH_2CH_2OPmb$, $R_Z = H$, R' = H, R = OBn, Y = H	72 h	-	**18b** 83%
19	$R_E = CH_2OBn$, $R_Z = H$, R' = BnO, R = H, Y = H	72 h	-	**19b** 86%
20	$R_E = CH_2OPmb$, $R_Z = H$, R' = OSiPr-i_3, R = H, Y = H	84 h	**20a** 36%	**20b** 58%
21	$R_E = CH_2OPmb$, $R_Z = H$, R' = H, R = OSiPr-i_3, Y = H	120 h	**21a** 30%	**21b** 63%
22	$R_E = H$, $R_Z = CH_2OPmb$, R' = H, R = OSiPr-i_3, Y = H	180 h	**22a** 17%	**22b** 66%
23	$R_E = CH_2OBn$, $R_Z = H$, R' = OSiPr-i_3, R = H, Y = SPh	20 h	-	**23b** 50%

Footnote: (a) Corrected for recovered **16** (50%), (b) corrected for recovered **17** (23%).



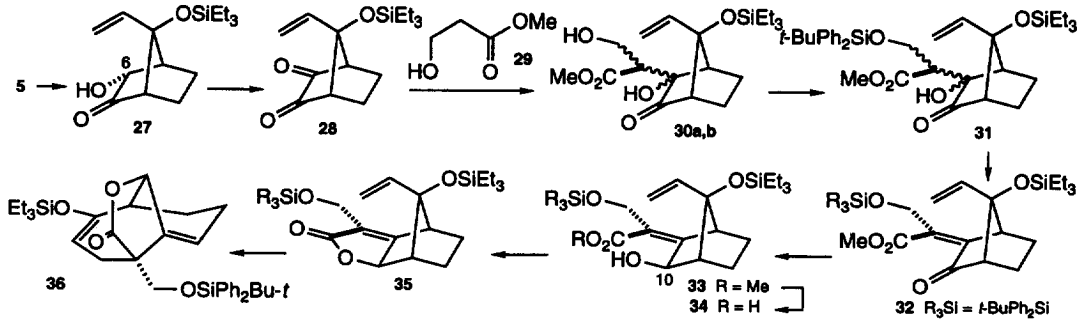
Scheme 2. (a) Prepared from **5**: LDA, THF, −78°C, 1 h; $BnOCH_2CHO$ (Shiao, M.-J. et al.[9]), 3 h; MsCl, Et_3N, CH_2Cl_2, 0°C, 1.5 h; DBU, THF, rt, 3 h; **24**, 32%, *E*-isomer, 41%. (b) $BnOCH_2SnMe_3$ (Hutchinson, D. K. et al.,[13] Bund, J. et al.,[14a] Boeckman Jr., R. K. and Cheon, S. H.[14b]) (BuLi, THF, −78°C, 15 min; then add to *i*-PrMgBr/CuBr·SMe_2, THF, −78°C, 20 min; then add **24** (*E* or *Z*), $BF_3 \cdot OEt_2$, keep at −45 to −50°C, 1.5 h; then add PhSeCl, THF, HMPA, 0°C, 4 h; 65%. Stereochemistry shown for **25** is an arbitrary assignment. (c) 30% H_2O_2, pyridine, CH_2Cl_2, 30°C, 1 h; 84%. (d) $LiBH_4$, $CeCl_3 \cdot 7H_2O$, THF–MeOH, 0°C, 1 h; 42% *endo* alcohol, 51% *exo* alcohol. (e) NaH, THF, 0°C, 15 min; BnBr, reflux, 20 h; 96% for **21**, 97% from *exo* alcohol

where the silyl enol ether is a significant product, selective desilylation of the $OSiEt_3$ group is easily effected under very mild conditions (e.g., THF, H_2O, AcOH, rt, 45 h; 85% for **20a**, 81% for **21a**).

We also examined the effect of placing a substituent at C(3) of the vinyl unit, as in **23**. Such a change would inter alia increase the proportion of conformers with C(4) oriented towards C(5) (see Table 1) and, from a synthetic point of view, might facilitate elaboration of the *siloxy*-Cope product. In the event, **23** rearranged in refluxing NMP faster than our other examples, and gave **23b** [50%, mixture of C(3) epimers], after 20 h (complete reaction).

Finally, it was necessary to establish if our oxy-Cope procedures were practical for making rearrangement products in which C(5) is not only quaternary but also carries a modifiable substituent — as a significant feature of **1** is full substitution at C(5). To this end, ketone **5** was hydroxylated (Scheme 3) at C(6) [**5** → **27**, LDA, THF, −78°C, 1 h; MoOPH, −23°C, 30 min; 85% (91% corrected for recovered **5**)] and oxidized (Dess–Martin reagent, CH_2Cl_2, 30 min; ca. 100%). Condensation of the resulting diketone **28** with the dianion derived from methyl 3-hydroxypropanoate[15] **29** (2 equiv. LDA, THF, −78°C, 40 min; add **28**, 10 min) gave two diastereoisomers, **30a** (39%) and **30b** (29%), whose stereochemistry was not established. Silylation of the major isomer (**30a** → **31**, *t*-$BuPh_2SiCl$, 3 h; 92%), followed by dehydration ($SOCl_2$, pyridine, 8 h; 91%) afforded the *Z*-olefin **32**, and reduction ($NaBH_4$, $CeCl_3 \cdot 7H_2O$,

MeOH, 0°C, 30 min, rt, 1.5 h) gave the desired *exo* alcohol **33** (69%) as well as the C(10) epimer (19%). Demethylation (PrSLi, HMPA, rt, 9 h; 83%) released the carboxyl group (**33** → **34**). Finally, cyclization (**34** → **35** was again (cf. **13**) easily achieved with 2-chloro-1-methylpyridinium iodide (Et_3N, CH_2Cl_2, reflux, 20 h; 65%, not optimized). When lactone **35** was heated in 1,2-dichlorobenzene it appeared (TLC control) to rearrange completely within 10 min and, after a further 10 min, **36** was isolated in ca. 100% yield.



Scheme 3.

In summary, we have found that NMP is a useful solvent for *siloxy*-Cope rearrangement, and we have demonstrated the effect of strain and substitution on the rearrangement of [2.2.1] bicyclic compounds of general type **17**. Several bridgehead olefins representing part of the CP-225,917 core have been made, including the tricyclic lactone **15**, and the first examples (**16b** and **36**) generated by the oxy-Cope route, with a quaternary C(5).

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada and Merck Frosst for financial support. V. G. holds an AHFMR Postdoctoral Fellowship.

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