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Synthesis of the racemic tetracyclic core of CP-225,917—a model compound lacking the sidearms of the natural product

Derrick L. J. Clive* and Shaoyi Sun

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

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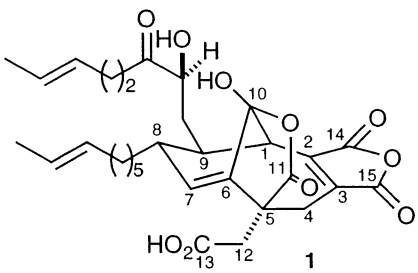
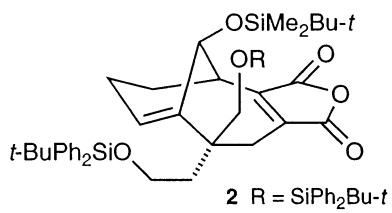
Abstract—Compound **3**, representing the tetracyclic core structure of CP-225,917, was prepared from bridgehead olefin **9**, which was first converted into ketone **13**. Peterson olefination then gave **15**, and this was elaborated into the anhydride **19**, from which crystalline **3** was reached by a sequence of deprotection and oxidation steps. © 2001 Elsevier Science Ltd. All rights reserved.

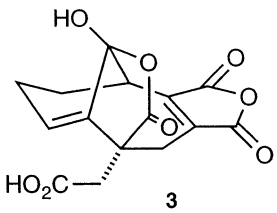
The synthesis of CP-225,917 (**1**) has attracted a great deal of attention, and there is substantial literature on the subject.[1–3] Previous reports[3] from this laboratory have described an approach based on an anionic oxy-Cope rearrangement,[3a] as well as various refinements of this process that take advantage of the individual or cumulative effects of solvent, substituents and, especially, strain.[3b] During these studies[3] several compounds were synthesized possessing certain characteristic features of the natural product, the most advanced model being **2**,[3d] which contains both the anhydride unit and the quaternary center. Here, we describe use of our method to make the complete tetracyclic core (**3**), i.e. a model lacking the two eight-carbon sidearms of CP-225,917.



1



2 R = $SiPh_2Bu$-*t*



3

In our previous work[3d] (see Scheme 1) we had elaborated the symmetrical diketone **4** into keto ester **7**, via hydroxy ester **6** (stereochemistry not established). The latter was made by treating diketone **4** with the carbanion derived from the γ-siloxy ester **5**. This reaction is a crucial step, as the stereochemical outcome ensures that the subsequent dehydration leads to the required *Z* olefinic ester **7**, from which the strained lactone **8** was easily made. We have not identified the features of **5** that are responsible for the high stereoselectivity in the conversion of **4** into **6**, but found that the carbanion derived from hydroxy ester **10** shows much lower selectivity (4:3) on reaction[3b] with a related symmetrical diketone. Lactone **8** undergoes efficient thermal siloxy-Cope rearrangement (99%) to the bridgehead olefinic lactone **9**, which was then elaborated into the model compound **2**.[3d] Subsequent attempts to convert **2** into the complete tetracyclic core (**3**) of the natural product were unsuccessful, but we now show how **9** can be elaborated in a different way, so as to produce **3**.

In our experience, intermediates potentially leading to systems resembling CP-225,917 often show anomalous behavior, and our earlier route[3d] to the anhydride segment required modification so as to accommodate the manipulations needed for oxidation at C(10); in particular, the method for introducing C(14) (cf. **1**), which had previously been accomplished smoothly with the Tebbe reagent, now had to be carried out by a modified Peterson reaction, as the Tebbe process gave a very low yield.

Keywords: Peterson reaction; anhydride; lactone; ruthenium dioxide; bridgehead olefin; quaternary carbon.

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

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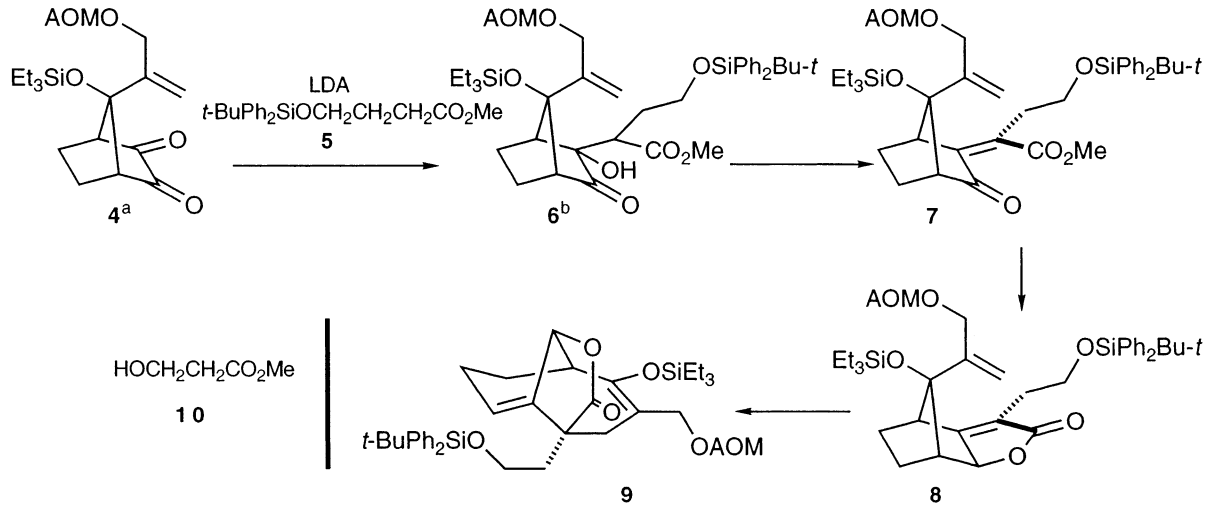


Scheme 1. [a] AOM = *p*-anisyloxymethyl, *p*-$MeOC_6H_4OCH_2$. [b] Stereochemistry not assigned.

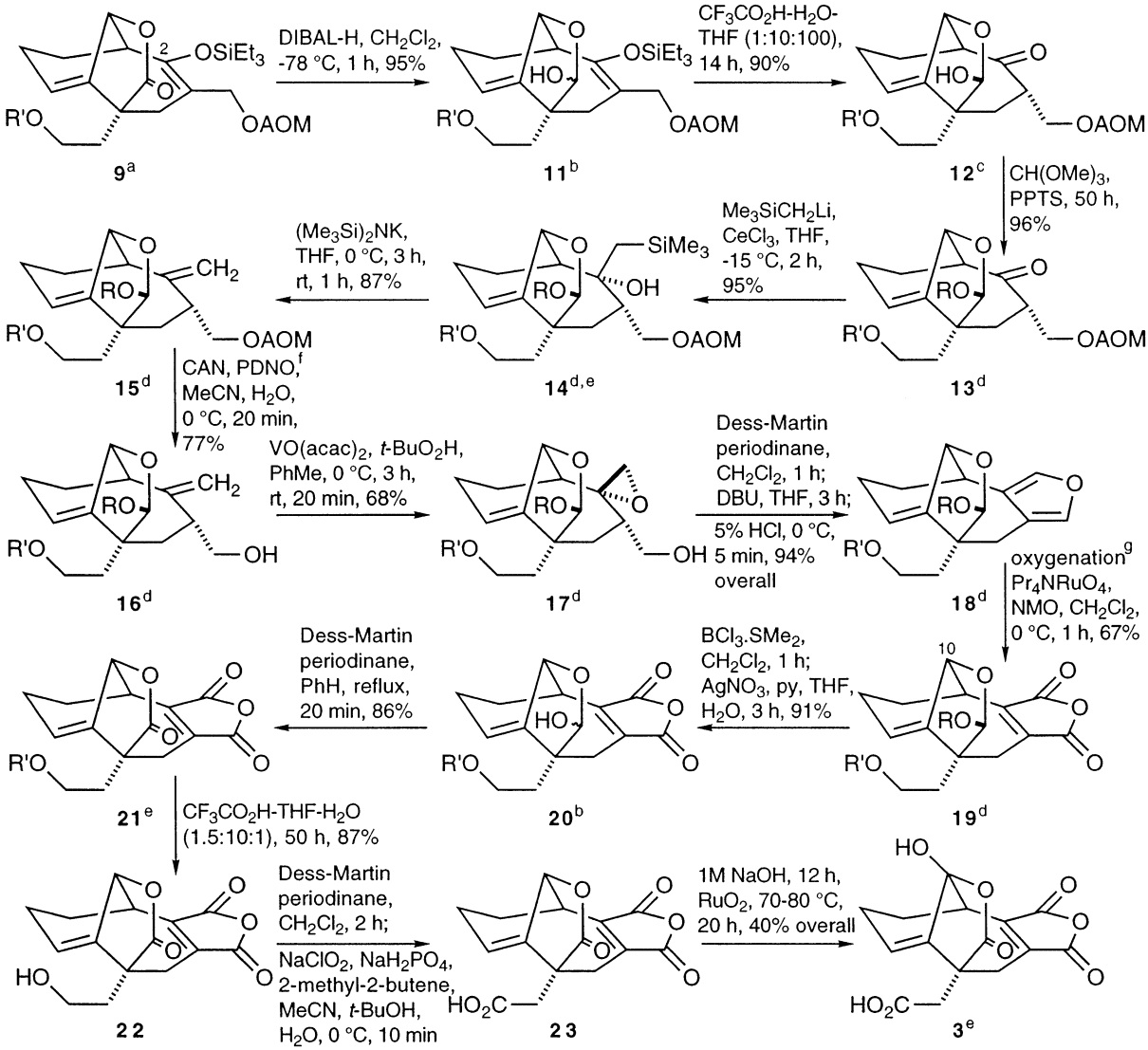
The first task was to protect the lactone carbonyl of **9** and liberate the C(2) ketone. To this end, **9** was treated with DIBAL-H to give (95%) lactols **11**, and exposure to aqueous CF_3CO_2H then served to convert the silyl enol ether into its corresponding ketone (**11**→**12**, 90%). Finally, the lactol was converted into its methyl ether by acid-catalyzed reaction with $CH(OMe)_3$ (**12**→**13**, 96%). At this point, we began to assemble the anhydride substructure. Introduction of the necessary additional carbon was effected by treatment of ketone **13** with 3 equiv. of a 1:1 mixture of Me_3SiCH_2Li and $CeCl_3$;[4] the product (**14**) was obtained (95%) in crystalline form, and X-ray analysis confirmed the gross structure and defined the stereochemistry. Reaction with $(Me_3Si)_2NK$ in THF at 0°C then completed the Peterson olefination, giving **15** in 87% yield. Attempts to remove the AOM group with $(NH_4)_2Ce(NO_3)_6$ did not work, but when the experiment was done in the presence of 2,6-pyridinedicarboxylic acid *N*-oxide—conditions that have been used for converting a phenol methyl ether into a quinone[5]—the required homoallylic alcohol **16** was formed in satisfactory yield (77%). Epoxidation under standard conditions [$VO(acac)_2$, *t*-BuO_2H, 0°C] gave epoxide **17**, to which we assign the indicated stereochemistry on the basis of mechanistic considerations. Oxidation of the primary hydroxyl to an aldehyde, using the Dess–Martin periodinane, exposure to DBU (to open the epoxide), and brief treatment with dilute hydrochloric acid (to effect dehydration) completed assembly of the furan **18** (94% overall). This was then converted into the anhydride (**18**→**19**) by sequential photooxygenation[6] and oxidation of the resulting hydroxy butenolides with the Pr_4NRuO_4 (catalytic)/NMO (stoichiometric) system,[7] the anhydride **19** being obtained in 67% yield.

At this point the remaining transformations were oxidation of the sidechain appended to the quaternary center, and introduction of oxygen at C(10) (see **19**). Based on experience gained by exploring a number of routes related to that summarized in Scheme 2, we decided to approach these tasks by regenerating the lactone subunit originally present in intermediate **9**, oxidizing the sidechain to the carboxylic acid, and then opening the lactone by hydrolysis. That last operation would expose the C(10) oxygen function as an alcohol, which we would then oxidize (in a basic medium) to the corresponding ketone—a substance that, under appropriate conditions, should spontaneously form the desired hemiacetal.

To regenerate the lactone, we treated lactol ether **19** with $BCl_3{\cdot}SMe_2$,[8] and obtained lactols **20** together with what we suspect is the corresponding unstable chloride (Cl instead of OH in **20**). When the total product from the demethylation was stirred (3 h) with aqueous $AgNO_3$ it was possible to isolate the desired lactols **20** in 91% yield, and Dess–Martin oxidation then regenerated the lactone (**20**→**21**, 86%); the structure of **21** was confirmed by X-ray analysis. Next, the sidechain oxygen was deprotected (**21**→**22**, aqueous CF_3CO_2H, 87%), and the resulting primary alcohol was oxidized first to the aldehyde (Dess–Martin periodinane), and then to the carboxylic acid ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene)[9] so as to obtain **23**, which was used crude. The material was stored for 12 h in 1 M NaOH at room temperature with the intention of opening the lactone and the anhydride, and the resulting salt, without isolation, was oxidized by addition of RuO_2[10] (70–80°C, 20 h). We were then able to isolate the tetracyclic core unit [**3**, mp 169°C (decomp.)] of CP-225,917 in 40% overall yield from **22**. The structure of **3** was confirmed by single crystal X-ray analysis.

These experiments provide for the first time the complete core unit, and serve as a model for more advanced work towards CP-225,917 itself.

All new compounds, except the aldehyde derived from **17**, the hydroxy butenolides derived from **18**, and acid **23** and its parent aldehyde, were characterized spectroscopically, including high resolution mass measurement.[11]



Scheme 2. [a] R′ = *t*-BuPh$_2$Si, AOM = *p*-anisyloxymethyl, *p*-MeOC$_6$H$_4$OCH$_2$. [b] Two isomers. [c] A single isomer; hydroxyl stereochemistry is an arbitrary assignment. Another isomer was also isolated (7% yield). [d] R = Me. [e] Structure determined by X-ray analysis. [f] CAN = $(NH_4)_2Ce(NO_3)_6$, PDNO = 2,6-pyridinedicarboxylic acid *N*-oxide. [g] Rose Bengal, *i*-Pr$_2$NEt (10 equiv.), CH_2Cl_2, O_2, −78°C, tungsten light, 20 h.

Acknowledgements

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11. Characterization data for key compounds: The symbols s′, d′, t′ and q′ in ^{13}C NMR spectra refer to 0, 1, 2 and 3 attached protons, respectively. Compound **14**: mp 132–135°C; FTIR (microscope) 2959, 2931, 2860, 1507, 1427, 1265 cm^{-1}; ^1H NMR (360 MHz, C_6D_6) δ 0.53 (s, 9H), 0.96 (d, $J=14.5$ Hz, 1H), 1.17–1.45 (m, 11H), 1.65 (t, $J=13.0$ Hz, 1H), 1.85–1.97 (m, 2H), 2.02–2.24 (m, 4H), 2.36–2.47 (m, 2H), 2.72–2.80 (m, 1H), 3.18 (s, 3H), 3.35 (s, 3H), 3.69 (dd, $J=9.6$ Hz, 2.9 Hz, 1H), 3.89–4.16 (m, 3H), 4.30 (br s, 1H), 4.54 (s, 1H), 4.90 (AB, $J=7.0$ Hz, 1H), 4.98 (AB, $J=7.0$ Hz, 1H), 5.14–5.22 (m, 1H), 6.68–6.74 (m, 2H), 6.82–7.00 (m, 2H), 7.20–7.31 (m, 6H), 7.80–7.93 (m, 4H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 0.80 (q′), 1.94 (s′), 21.9 (t′), 22.5 (t′), 27.1 (q′), 33.2 (s′), 34.5 (t′), 41.3 (t′), 43.1 (d′), 46.2 (d′), 50.5 (s′), 54.0 (d′), 55.1 (q′), 61.6 (t′), 73.0 (t′), 78.0 (t′), 81.6 (q′), 93.7 (t′), 110.5 (d′), 114.2 (d′), 115.0 (d′), 117.1 (d′), 127.9 (d′), 129.9 (d′), 134.3 (s′), 134.6 (s′), 136.0 (d′), 146.1 (s′), 151.6 (s′), 155.2 (s′); exact mass (HR electrospray) m/z calcd for $C_{43}H_{60}NaO_7Si_2$ (M+Na) 767.377531, found 767.377667. Compound **18**: mp 129–131°C; FTIR (CH_2Cl_2, cast) 3069, 3047, 2929, 2893, 1651, 1588, 1530, 1427, 1094 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.12–1.24 (m, 10H), 1.60–1.83 (m, 3H), 1.94–2.15 (m, 2H), 2.40–2.55 (m, 1H), 2.87 (d, $J=14.6$ Hz, 1H), 3.16 (s, 3H), 3.29–3.42 (m, 1H), 3.87–4.02 (m, 2H), 4.40–4.54 (m, 1H), 4.57 (s, 1H), 5.33–5.42 (m, 1H), 6.91–7.02 (m, 2H), 7.08–7.30 (m, 6H), 7.77–7.85 (m, 4H); ^{13}C NMR (50.3 MHz, C_6D_6) δ 19.3 (s′), 22.2 (t′), 27.1 (q′), 29.5 (t′), 34.7 (d′), 35.4 (t′), 37.8 (t′), 51.6 (s′), 54.1 (d′), 61.6 (t′), 79.3 (q′), 110.6 (d′), 115.7 (d′), 121.9 (s′), 128.1 (d′), 129.9 (d′), 134.2 (s′), 134.4 (s′), 136.0 (d′), 140.1 (d′), 140.6 (d′), 149.1 (s′); exact mass (HR electrospray) m/z calcd for $C_{32}H_{38}NaO_4Si$ (M+Na) 537.243708, found 537.243841. Compound **19**: FTIR (CH_2Cl_2 cast) 2930, 2856, 1847, 1763, 1427, 1103 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.98–1.13 (m, 1H), 1.25 (s, 9H), 1.40–1.68 (m, 3H), 1.71–1.83 (m, 1H), 1.95 (dd, $J=7.6$ Hz, 1.7 Hz, 1H), 2.18–2.32 (m, 1H), 2.75 (d, $J=7.6$ Hz, 1H), 3.00–3.14 (m, 4H), 3.75–3.84 (m, 2H), 4.13 (br s, 1H), 4.38 (s, 1H), 4.97–5.04 (m, 1H), 7.18–7.33 (m, 6H), 7.77–7.85 (m, 4H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 19.3 (s′), 21.5 (t′), 23.7 (t′), 27.1 (q′), 34.6 (t′), 37.8 (d′), 38.9 (t′), 50.6 (s′), 54.0 (d′), 61.1 (t′), 77.7 (q′), 110.2 (d′), 116.2 (d′), 128.1 (d′), 130.0 (d′), 130.1 (d′), 133.8 (s′), 134.0 (s′), 135.9 (d′), 141.4 (s′), 143.3 (s′), 146.7 (s′), 166.2 (s′), 166.5 (s′); exact mass (HR electrospray) m/z calcd for $C_{32}H_{36}NaO_6Si$ (M+Na) 567.217887, found 567.218614. Compound **21**: mp 156–158°C; FTIR (microscope) 3566, 3052, 2926, 2879, 1854, 1785, 1762, 1472, 1251, 1086, 1058 cm^{-1}, ^1H NMR (200 MHz, C_6D_6) δ 0.64–0.90 (m, 1H), 1.23 (s, 9H), 1.25–1.61 (m, 4H), 1.87 (dd, $J=18.9$, 1.9 Hz, 1H), 2.21–2.40 (m, 1H), 2.83 (d, $J=18.9$ Hz, 1H), 3.07 (br s, 1H), 3.50–3.72 (m, 2H), 4.20–4.38 (m, 1H), 4.71–4.93 (m, 1H), 7.16–7.35 (m, 6H), 7.60–7.88 (m, 4H); ^{13}C NMR (50.3 MHz, C_6D_6) δ 19.3 (s′), 20.9 (t′), 23.4 (t′), 26.8 (q′), 34.6 (t′), 38.1 (d′), 41.9 (t′), 46.7 (s′), 60.2 (t′), 77.6 (d′), 119.6 (d′), 128.2 (d′), 130.0 (d′), 130.1 (d′), 133.4 (s′), 133.8 (s′), 135.8 (d′), 136.0 (s′), 138.2 (s′), 141.1 (s′), 143.5 (s′), 165.3 (s′), 178.0 (s′); exact mass (HR electrospray) m/z calcd for $C_{31}H_{32}NaO_6Si$ 551.186587, found 551.186076. Compound **3**: FTIR (acetone cast) 2924, 1958, 1766, 1696, 1685, 1268, 988 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 1.64–1.74 (m, 1H), 2.23–2.44 (m, 2H), 2.51–2.61 (m, 1H), 2.82 (s, 2H), 3.13 (AB q, $J_{AB}=17.8$ Hz, $\Delta\nu_{AB}=13.0$ Hz, 2H), 3.65 (dd, $J=8.3$, 1.4 Hz, 1H), 6.02–6.45 (br signal including dd, $J=8.1$, 3.6 Hz, 3H in all); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 21.5 (t′), 23.4 (t′), 37.2 (t′), 40.6 (t′), 44.1 (d′), 49.2 (s′), 105.5 (s′), 125.3 (d′), 139.3 (s′), 142.5 (s′), 144.7 (s′), 166.4 (s′), 166.7 (s′), 171.5 (s′), 176.6 (s′); exact mass (HR electrospray) m/z calcd for $C_{15}H_{12}NaO_8$ (M+Na) 343.042987, found 343.042519.