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DICOBALTOCTACARBONYL–ALKYNE COMPLEXES AS INTERMEDIATES IN THE SYNTHESIS OF BICYCLO[3.3.0]OCTENONES FOR THE SYNTHESIS OF CORIOLIN AND HIRSUTIC ACID

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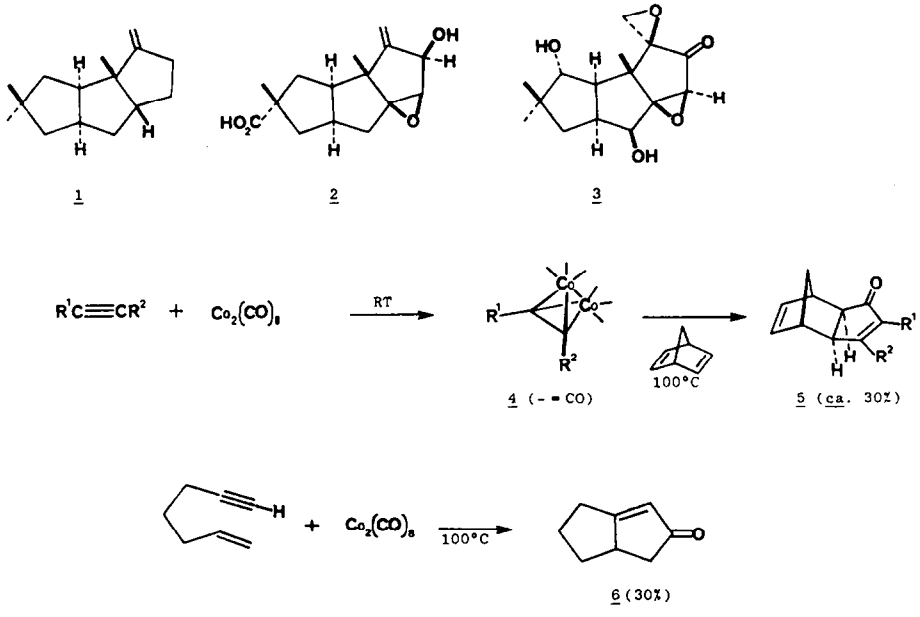
Abstract—Treatment of the readily prepared enzynes **12**, **21** and **45** with $Co_2(CO)_8$ at *ca* 110° results in high yields (80%) of substituted bicyclo[3.3.0]octenones, that are suitable for straightforward elaboration into coriolin and hirsutic acid precursors. A mechanistic hypothesis to explain the observed stereospecificity is presented.

During recent years there has been an increasing interest in the application of transition metal mediated organic reactions for the synthesis of natural products.[1] This heightened interest is based primarily upon the unusual selectivity and reactivity associated with such reactions, which is not found in their classical organic reaction counterparts. Obviously, if transition metal mediated organic reactions are to find widespread general use in the synthesis of natural products, it is essential that they simplify complicated problems, and of course, be experimentally convenient. Here we report the details of some alkyne–alkene–carbon monoxide insertion reactions, mediated by the inexpensive dicobaltoctacarbonyl, for the synthesis of specific functionalized bicyclo[3.3.0]octenones.[2]

A great deal of effort has been devoted to the synthesis of natural products containing three linearly fused 5-membered rings, namely the tricyclo[6.3.0.$0^{2,6}$]undecane system.[3] Representative examples are hirsutene **1**, hirsutic acid **2** and the antibiotic coriolin **3**, all of which have been synthesized.[4] Our own interest in this area started with organosilicon chemistry, and produced a new cyclopentenone annulation reaction which resulted in a synthesis of hirsutene **1**.[5] It was quite apparent that this type of annulation reaction, based upon a Lewis acid mediated Nazarov reaction of a phenylthio-substituted vinyltrimethylsilane, would not be applicable to the more highly substituted, and sensitively functionalized systems, such as coriolin **3**.

A reaction that seems to hold great promise, and as yet has been relatively unexploited in natural product synthesis, is the dicobaltoctacarbonyl mediated insertion of an alkene into an alkyne with concomitant CO insertion to give a cyclopentenone in one step (Scheme 1). Pausen and Khand, in the early 1970s, described several examples of this reaction.[6] In particular, they established that the yields of



Scheme 1.

cyclopentenones are improved if the alkene is strained, and the reaction is regiospecific (the larger group attached to the alkyne ends up adjacent to the newly inserted CO group), and finally the cyclopentenone **5** is *exo*-(**4–5**). Recently, Shore reported an intramolecular version of the Pausen–Khand reaction to make **6**.[7] Dicobalt hexacarbonyl complexes of acetylenes are well-known,[8] readily made, stable compounds, whose structures are represented by the general formula **4**, where the two cobalt atoms cap the acetylene triple bond to form a tetrahedral bimetallo-cluster.[9]

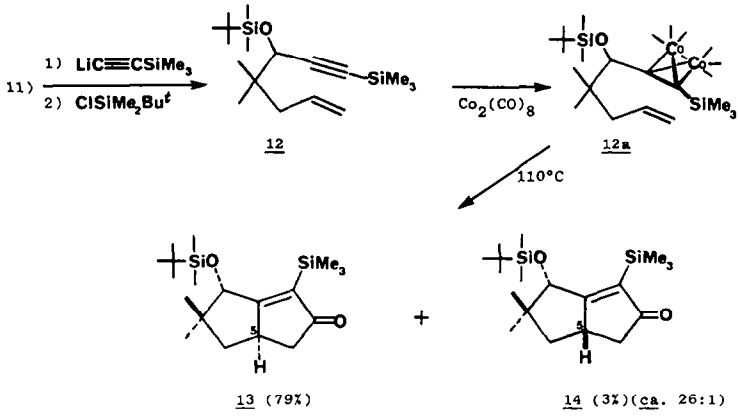
While the yields of the cyclopentenones, whether formed inter- or intramolecularly, are relatively modest, we felt that this could be easily improved by the choice of appropriate substituents connecting the alkyne to the alkene. If successful, the cobalt mediated process could become a highly convergent way of synthesizing functionalized bicyclo[3.3.0]octenones for the synthesis of coriolin **3** and hirsutic acid **2**. In this regard, it is also important to ascertain the stereospecificity of the cyclization process, with respect to adjacent substituents (1,2- and 1,3-induction) to the newly formed stereocenter at the ring-fusion. Scheme 2 outlines a retrosynthetic pathway for the synthesis of coriolin **3**, that is based upon the $Co_2(CO)_8$–alkyne–alkene reaction.

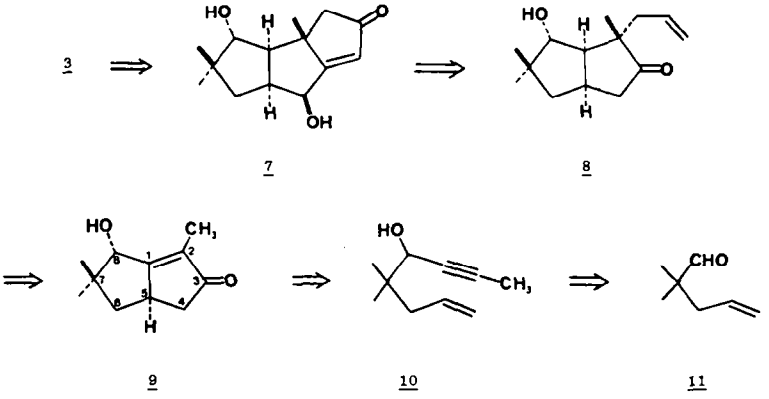
Scheme 2 illustrates the inherent simplicity of this strategy, whereby the relatively complicated bicyclo-[3.3.0]oct-2-en-3-one **9** may be constructed from very simple acyclic precursors, **10**/**11**, in a single step. Undoubtedly, the $Co_2(CO)_8$ mediated conversion of **10** into **9** should greatly benefit from the *gem*-methyl group (Thorpe–Ingold effect),[10] and for this reason we did not carry out any model studies, but proceeded directly with the substrates needed for the synthesis of coriolin **3**, and a bicyclo[3.3.0]octenone precursor to hirsutic acid **2**.

RESULTS

The aldehyde **11** is readily available in multigram quantities from isobutanal and allyl alcohol *via* a Claisen rearrangement.[11] Treatment of **11** with lithium(trimethylsilyl)acetylide in THF at −70°, followed by *in situ* protection of the generated lithium alkoxide with $ClSiMe_2Bu^t$ gave the required trimethylsilyl acetylene adduct **12** in overall 86% yield from **11**. We initially chose to have the terminal acetylene protected by the relatively bulky trimethylsilyl group to minimize any oligomerization side reactions, in particular, trimerization to benzenoid compounds.[12] The enyne **12** was treated with $Co_2(CO)_8$ in heptane at 110° in a resealable tube under a slight positive pressure of CO. After 20 hr the cobalt hexacarbonyl complex **12a** was completely consumed (in general, complexes of the **12a** type are air stable red compounds that can be chromatographed without any special precautions), and after work-up the bicyclo[3.3.0]octenone **13** (79%), along with the minor 5-epimer **14** (3%), was isolated.

The proof of the relative stereochemistry of **13** rests on the following chemical and physical evidence. Hydrogenation of **13** (10% Pd/C) gave a single saturated ketone **15** (89%, m.p. 59–62°), which on treatment with HBF_4/THF/20° gave the desilylated alcohol **16** (87%, m.p. 70.5–71.5°). The derived ethylene ketal **17** (92%), on oxidation (DMSO/oxalyl chloride/CH_2Cl_2/−50°) gave the ketone **18** (67%). The





Scheme 2.

purpose of this sequence is to allow access to the epimeric alcohol **19** for comparison purposes. Reduction of **18** gave mixtures of **17** and **19**, in the ratios given in Table 1.

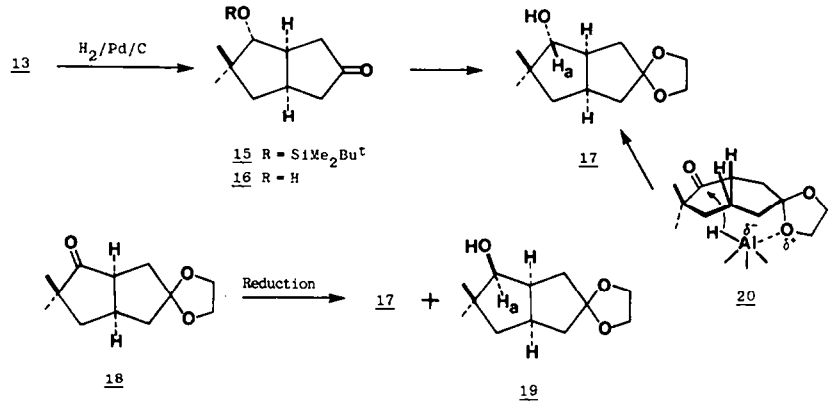
Normally, reduction of bicyclo[3.3.0]octanones of the type **18**, but without the ethylene ketal functional group, are reduced from the *exo*-face to give the *endo*-alcohol.[3] The surprising amount of *exo*-alcohol **17**, especially in the case of $LiAl(OBu^t)_3H$ reduction, presumably is the result of coordination of the reducing agent to the ketal oxygen atoms, which for *endo*-coordination **20** can deliver hydride intramolecularly. The most important result is the Li/NH_3 reduction of **18** to give predominantly the thermodynamically more stable *exo*-alcohol **17**. By analogy with the results obtained by Danishefsky and Ikegami,[4] in their respective syntheses of coriolin **3**, this allows the assignment of relative configuration to **17** as shown, and correspondingly **13** and **14**. The ^{1}H-NMR spectrum of **17** shows H_a(d) $J = 7$ Hz, and for **19**, H_a(d) $J = 4.5$ Hz.

In summary, the bicyclo[3.3.0]octenone **13** is available in a single step in 79% yield in a stereoselective $Co_2(CO)_8$ mediated cyclization of the simple, readily available, acyclic enyne **12**. We will speculate on the origins of the observed stereoselectivity later.

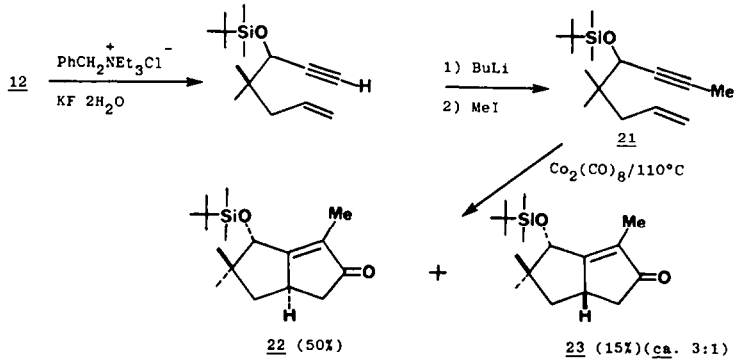
In order to explore the $Co_2(CO)_8$ mediated enyne cyclization further, and in particular its stereoselectivity, we examined the synthesis of the tricyclic enone **7**, which has been converted by Trost[4] into the penultimate intermediate in Danishefsky's synthesis of coriolin **3**.

Treatment of **12** with $PhCH_2^+NEt_3Cl^-/KF \cdot 2H_2O/THF$,[13] heated at reflux (3 hr), followed by n-BuLi/MeI $-70°$ to $20°$ gave **21** (87%). Exposure of **21** to $Co_2(CO)_8/CO$/heptane/110°/20 hr in a resealable tube gave the bicyclo[3.3.0]octenone **22** (50%), along with its readily separated C-8 epimer **23** (15%). Running the same reaction as above except in an open system (atmospheric pressure) gave **22** (41%) and **23** (12%), and using the $Co_2(CO)_8$ catalytically (0.1 equiv, sealed tube set-up) gave only **22** (20%). The decrease in yield (*ca* 17%), and marked decrease in stereoselectivity (26 : 1 to 3 : 1), between the cyclization of **12** and **21**, should be noted.

Hydrogenation of **22** (10% Pd/C) gave **24** (92%), which was treated with NaH/DME/allyl bromide/60° to give the bicyclo[3.3.0]octenone **25** (79%). Wacker oxidation ($PdCl_2$ cat./CuCl/O_2/DMF/H_2O) gave the 1,4-diketone **26** (64%), which on treatment with $KOBu^t/Bu^tOH$/20°/10 min gave the tricyclic enone **27** (74%). Deconjugation of **27** by exposure to $KOBu^t$ (10 equiv)/Bu^tOH/DME/20° for 2 hr, followed by work up with aqueous AcOH gave the labile β,γ-unsaturated ketone **28**. Epoxidation of **28** using MCPBA (1.0 equiv)/CH_2Cl_2/20° gave the *cis*-epoxide **29**, maintaining a *cis*-fusion between the two adjacent 5-membered rings. When **29** was exposed to DBU/CH_2Cl_2/20° the

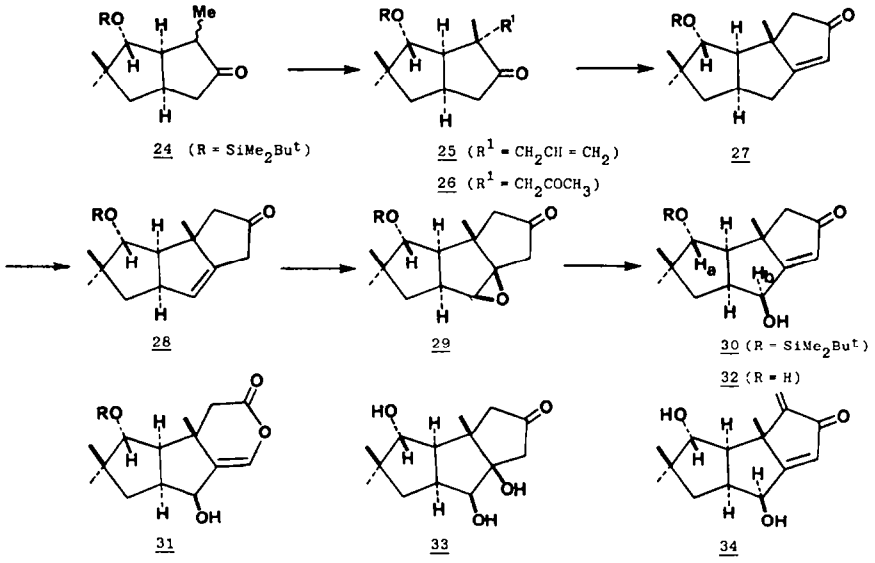


REDUCING AGENT	RATIO OF 17 TO 19
$LiAlH_4$/THF/0°C	2:1
$NaBH_4$/EtOH/20°C	6:5
$LiAl(OBu^t)_3H$/THF/20°C	2:3
Li/NH_3/THF	9:1



required γ-hydroxy-cyclopentenone **30** was isolated in overall 34% yield from **27**. If excess MCPBA is present in the conversion of **28** into **29**, the lactone **31** can be isolated after DBU treatment.

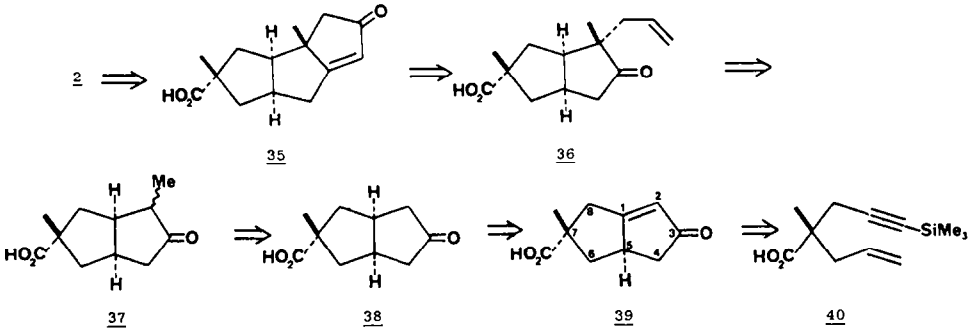
Deprotection of **30** using 25% aqueous HBF_4/THF gave **32**, contaminated with the triol **33** (4 : 1), whereas, treatment of **30** with poly HF/pyridine/THF avoided this complication and gave **32** (74%, m.p. 156–158°); H_a(d) J = 9 Hz, and H_b(d) J = 6 Hz, *cf* **17** and **19**. (**32** was compared with an authentic sample, kindly supplied by Professor B. M. Trost, and they were identical in all respects.) Since **32** has been converted into **34** by Trost,[4] and Danishefsky[4] has conducted the final transformation of the cyclopentadienone **34** into coriolin **3** itself, the preparation of **32** constitutes a synthesis of coriolin.



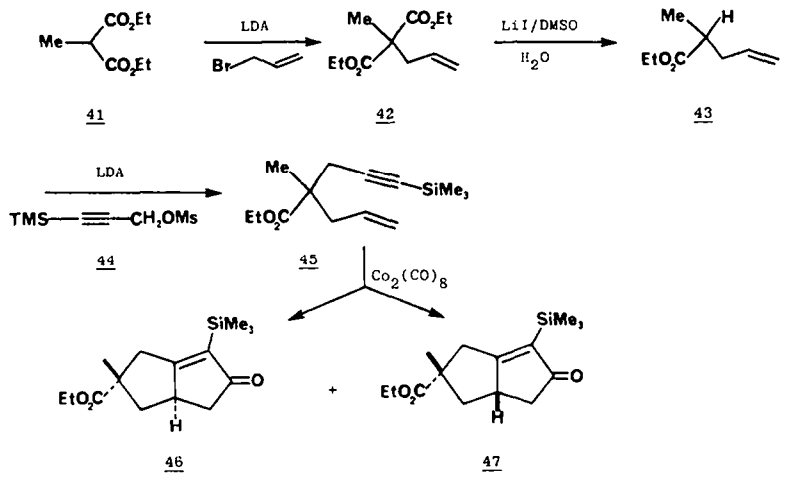
A similar strategy to that used for the synthesis of coriolin **3** can be used to construct a precursor for the synthesis of hirsutic acid **2**. Scheme 3 outlines the retrosynthetic pathway. The tricyclic ketone **35** had been converted into hirsutic acid **2** by a number of groups. Matsumoto[4] showed that the bicyclic ketone **37** (as the methyl ester) could be transformed into **35** by allylation, Wacker oxidation and treatment with base. This sequence is identical to the procedures used for coriolin **3**. The symmetrical ketone **38** is the key intermediate in the synthesis, and was made in a non-stereospecific manner. Using the $Co_2(CO)_8$ cyclization strategy the bicyclic[3.3.0]oct-2-en-3-one **39** is the crucial target, and should, in principle, be directly available in a single step from the acyclic enyne **40**. The most important question to be answered in this approach is the degree of stereoselectivity in establishing the correct *syn*-relationship between the $-CO_2H$ group at C-7, and the newly formed ring fusion. It is somewhat ironic to note that, while a considerable effort has been expended in either controlling the stereochemistry at C-5 relative to the $-CO_2H$ group, or separating epimers of **38**, in fact, C-5 in the enone **39** is an epimerizable position *via* acid or base catalyzed equilibration. Consequently, while it would be highly desirable to have a completely stereospecific conversion of **40** into **39**, it is not imperative if efficient equilibration of C-5 is experimentally possible.

The required enyne **41** was made by straightforward alkylation chemistry. Treatment of diethyl methylmalonate with LDA/THF/−70° to 0°, followed by allylbromide, gave **42** (99%), which was directly decarboethoxylated with LiI/DMSO/H_2O/180° to give the ester **43** (72%).[14] Alkylation of **43** using LDA/THF/0° to 20°, followed by the propargyl mesylate **44**, gave the required enyne-ester **45**. Exposure of **45** to $Co_2(CO)_8$/120°/25 hr, followed by chromatography over florisil, gave a separable mixture of **46** and **47** (86% isolated yield, ratio 55 : 45).

The almost complete lack of stereoselectivity was not



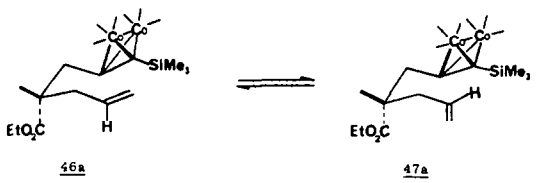
Scheme 3.



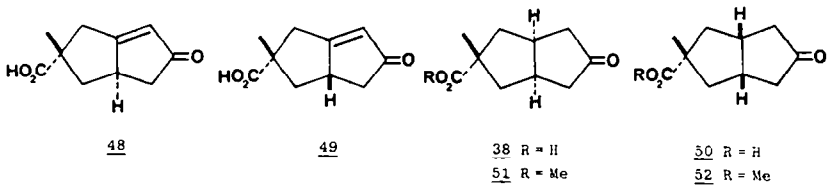
wholly unexpected, since the steric differentiation between the 7-Me and 7-CO_2Et group is not sufficiently pronounced to cause an overwhelming energy difference between the two conformers **46a/47a**.

Speculated mechanism and stereoselectivity

Scheme 4 summarizes a working mechanistic hypothesis. The isolable complex **53** can form two cobalt metallocycles **54** and/or **55** on alkene insertion



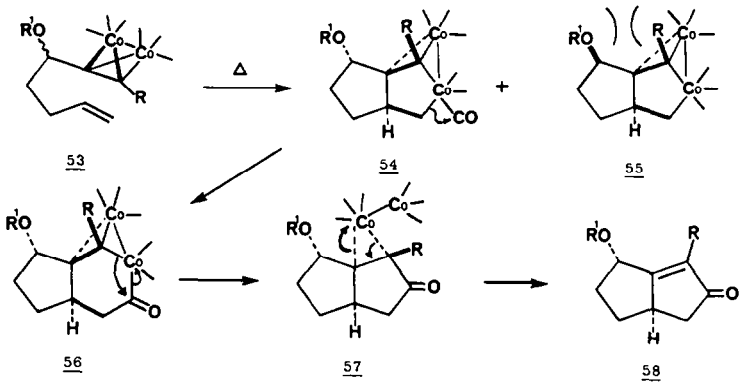
(It should be noted that the complex between **45** and $Co_2(CO)_8$, **46a/47a** is an air-stable chromatographable compound.) The isomer **46**, with the correct relative configuration between C-5 and C-7, has δ 1.46 (3H, s). Treatment of the mixture of **46** and **47** with 35% aqueous methanesulfonic acid at 75° for 2.25 hr, followed by aqueous work-up, gave the isomeric acids **48** and **49** (1.34:1, 96% yield). (Note: the $-SiMe_3$ group is lost.) Further exposure of the acids **48** and **49** into the internal C—Co bond. The newly formed 5-membered ring Co-metallocycle is presumably *cis*-fused. Since we know that the substituent attached to the terminus of the acetylene has a dramatic effect on the stereochemical outcome of the reaction, it must be implicated in the intermediates or transition state(s). The metallocycle **54** minimizes the steric interactions between R^1O- and R—, whereas, **55** has a severe 1,3-pseudodiaxial interaction on the *endo*-face.



to various equilibrating conditions such as TsOH. H_2O/benzene/80° gave **48/49** (1.68:1 ratio). The readily separated acids **48** and **49** were hydrogenated (H_2/10% Pd/C) to give **38** and **50** respectively, which were treated with diazomethane to give the corresponding methyl esters **51** and **52**. The ^{1}H-NMR spectrum of **51** corresponded to the data reported by Matsumoto (Experimental section).[4] The epimer **49** can be re-equilibrated (TsOH · H_2O) into **48/49**, and in this way **48** is available from **46** and **47** in over 90% stereoselectively through three cycles of the equilibration process.

In summary, the bicyclo[3.3.0]octanone **38/51** is available in six steps from diethyl methyl malonate, and three steps from the enyne **45**. This sequence provides the most efficient and convenient synthesis of **51**, the Matsumoto precursor to hirsutic acid.

Consequently, large R— groups ($-SiMe_3$) would be expected to strongly favor **54**, which is in keeping with the observed trends. The metallocycle **54** can undergo CO— insertion to the acyl—Co complex **56**, which is set up to migrate the C—Co bond to the adjacent electrophilic carbonyl group to give **57**. Reductive elimination of the cobalt carbonyl residue in **57** establishes the cyclopentenone double bond.[15] This mechanistic hypothesis predicts that substituents at C-7 (hirsutic acid) would not have any pronounced preference for either the *exo*- or *endo*-configuration (which is the case). It also predicts that substituents at C-6 should prefer to be situated on the *exo*-face of the resulting bicyclo[3.3.0]octenone. We are currently examining the latter prediction in relation to prostacycline analogs and sesquiterpene synthesis.



Scheme 4.

CONCLUSIONS

The $Co_2(CO)_8$ mediated cyclization of relatively simple enynes provides a compellingly direct route to bicyclo[3.3.0]octenones. The yields are high (*ca* 80%), which combined with a useful stereoselectivity has lead to a short synthesis of coriolin **3**, and a direct synthesis of precursors that have been converted into hirsutic acid **2**.

EXPERIMENTAL

The general protocols followed in the experimental procedures have been described in detail elsewhere.[16]

1-Trimethylsilyl-3-(dimethyl-t-butylsilyloxy)-4,4-dimethyl-hept-6-ene-1-yne **12**

To a soln of trimethylsilylacetylene (9.1 g) in dry THF (100 ml) at −70° under argon, was added a 1.55 M soln of n-BuLi in hexane (52.5 ml). After 1 hr at −70° a soln of 2,2-dimethylpent-4-enal[11] (8.7 g) in THF (2 ml) was added, and the mixture maintained at −70° for 1 hr. A soln of t-BuMe$_2$SiCl (12.85 g) in dry THF (25 ml) was added to the above mixture, and the mixture heated at reflux for 20 hr. The THF soln was concentrated to *ca* 50 ml *in vacuo*, water (100 ml) was added and the mixture extracted with ether (3 × 100 ml). The combined extracts were washed with sat NaCl aq (25 ml), dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was chromatographed on florisil eluting with light petroleum, and further purified by distillation under reduced pressure to give **12** (21.7 g, 86%), b.p. 96–98°/0.9 mm Hg. IR ($CHCl_3$) 2155 and 1635 cm^{-1}. NMR (90 MHz) δ 0.09 (3H, s), 0.14 (12H, s), 0.88 (15H, s), 2.08 (2H, d, J = 7 Hz), 4.00 (1H, s), 4.87–5.19 (2H, m), 5.60–6.10 (1H, m). (Found: C, 66.47; H, 11.45. $C_{18}H_{36}OSi_2$ requires: C, 66.59; H, 11.18%.)

Standard procedure for $Co_2(CO)_8$ mediated cyclizations

To a soln of $Co_2(CO)_8$ (1.0 equiv) in dry heptane (purged with CO for 2 hr) at 20° was added a soln of the enyne (1.0 equiv). CO was passed through the mixture for a further 1 hr and the vessel sealed (screw-top sealed pyrex tube), and heated to 110° for 20 hr. After cooling to 20° the mixture was transferred to a florisil column and eluted with light petroleum to remove $Co_2(CO)_8$. Elution with various Et_2O/petrol mixtures gave the bicyclic[3.3.0]enone adducts, which were further purified by bulb-to-bulb distillation under reduced pressure.

2-Trimethylsilyl-5αH-7,7-dimethyl-8α-(dimethyl-t-butylsilyloxy)bicyclo[3.3.0]oct-2-en-3-one **13**, *and its 5βH-epimer* **14**

Treatment of **12** (500 mg, 1.54 mmol) with $Co_2(CO)_8$ (540 mg, 1.58 mmol) in heptane (8 ml) at 110° for 20 hr gave **13** (430 mg, 79%) b.p. 125°/0.6 mm Hg (R_f, florisil 0.23 in 1:19 Et_2O/petrol). IR ($CHCl_3$) 1685 and 1615 cm^{-1}. NMR (220 MHz) $CDCl_3$ δ 0.02 (3H, s), 0.12 (3H, s), 0.21 (9H, s), 0.76 (3H, s), 0.87 (9H, s), 0.98–1.14 (1H, m), 1.91–2.12 (2H, m), 2.66 (1H, dd, J = 18 and 7 Hz), 3.30–3.44 (1H, m), 4.16 (1H, s). (Found: C, 64.48; H, 10.02%. $C_{19}H_{36}O_2Si_2$ requires: C, 64.71; H, 10.29.) The 5β-epimer has R_f, florisil 0.11 in 1:19 Et_2O/petrol. IR ($CHCl_3$) 1690 and 1595 cm^{-1}. NMR (220 MHz) δ 0.12 (3H, s), 0.13 (3H, s), 0.21 (9H, s), 0.78 (3H, s), 0.92 (9H, s), 1.13 (3H, s), 1.17–1.30 (1H, m), 1.74–2.06 (2H, m), 2.54 (1H, dd, J = 16 and 8 Hz), 2.74–2.90 (1H, m), 4.72 (1H, s). Compound **14** (16 mg, 3%) b.p. 125°/0.6 mm Hg.

7,7-Dimethyl-8-(dimethyl-t-butylsilyloxy)-cis-bicyclo[3.3.0]octan-3-one **15**

To a soln of **13** (480 mg, 1.14 mmol) in 95% EtOH (20 ml) at 20° was added 10% Pd/C (20 mg) and the mixture hydrogenated in the usual manner. The resulting mixture was filtered through celite, washed with EtOH, and evaporated *in vacuo*. The residue was chromatographed over silica gel (60H) to give **15** (286 mg, 89%), m.p. 59–62°. IR ($CHCl_3$) 1750 cm^{-1}. NMR (220 MHz) $CDCl_3$ δ −0.08 (3H, s), −0.07 (3H, s), 0.76 (9H, s), 0.79 (3H, s), 0.84 (3H, s), 0.94–1.10 (1H, m), 1.75–1.92 (2H, m), 1.98–2.17 (1H, m), 2.31–2.58 (3H, m), 2.58–2.81 (1H, m), 3.27 (1H, d, J = 7 Hz). (Found: C, 68.13; H, 11.00%. $C_{16}H_{30}O_2Si$ requires: C, 68.03; H, 10.70.) The 8β-epimer (prepared by hydrolysis of **19**, followed by silylation) has 0.00 (3H, s), 0.01 (3H, s), 0.83 (9H, s), 0.91 (3H, s), 0.95 (3H, s), 1.39 (1H, dd, J = 13 and 7 Hz), 1.77 (1H, dd, J = 13 and 8 Hz), 1.91–2.08 (1H, m), 2.12 (1H, dd, J = 19 and 10 Hz), 2.36–2.53 (2H, m), 2.62–2.83 (1H, m), 2.84–3.00 (1H, m), 3.57 (1H, d, J = 4.5 Hz).

7,7-Dimethyl-8α-hydroxy-cis-bicyclo[3.3.0]octan-3-one **16**

To a soln of **15** (250 mg, 0.89 mmol) in THF (10 ml) was added 25% aq HBF_4 (2.5 ml) in one portion. After 4 hr at 20°, water (10 ml) and $CHCl_3$ (10 ml) was added and the aqueous layer separated and further extracted with $CHCl_3$ (2 × 10 ml). The combined extracts were washed with sat $NaHCO_3$ aq (10 ml), and sat NaCl aq (10 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed over florisil eluting with EtOAc/petrol (1:1) to give **16** (130 mg, 87%), m.p. 70.5–71.5°. IR ($CHCl_3$) 3615, 3450 and 1735 cm^{-1}. NMR (220 MHz) $CDCl_3$ δ 0.94 (3H, s), 1.14–1.26 (1H, m), 1.86–2.08 (2H, m), 2.30 (1H, d, J = 17 Hz), 2.45–2.91 (4H, m), 3.04 (1H, bs), 3.35 (1H, bd, J = 5.5 Hz). (Found: C, 71.14; H, 9.50%. $C_{10}H_{16}O_2$ requires: C, 71.39; H, 9.59.) The 8β-epimer has m.p. 79–81°. δ 0.95 (3H, s), 1.08 (3H, s), 1.48 (1H, dd, J = 14 and 6 Hz), 1.85–2.35 (3H, m), 2.14 (1H, 1H, bs), 2.44–2.64 (2H, m), 2.74–3.08 (2H, m), 3.61 (1H, bt).

7,7-Dimethyl-8α-hydroxy-cis-bicyclo[3.3.0]octan-3-ethylene ketal **17**

A mixture of **16** (60 mg, 3.57 mmol) and the ethylene ketal of butan-3-one (2.07 g, 17.8 mmol) in benzene (50 ml) containing

TsOH · H_2O (5 mg) was heated at reflux for 3 hr with provision for the removal of water (Dean and Stark). Work-up in the usual way gave **17** (693 mg, 92%). IR ($CHCl_3$) 3610 and 3460 cm^{-1}. NMR (220 MHz) $CDCl_3$ δ 0.84 (3H, s), 0.97 (3H, s), 1.27 (1H, dd, J = 12 and 10 Hz), 1.50 (1H, dd, J = 14 and 4 Hz), 1.65–2.06 (4H, m), 2.25–2.45 (1H, m), 2.45–2.67 (1H, m), 2.93 (1H, s), 3.42 (1H, d, J = 8 Hz), 3.80–4.00 (4H, m). R_f (silica) 0.21 (1:1 EtOAc/petrol). This material was used directly in the oxidation–reduction experiments.

7,7 - Dimethyl - 8 - oxo - cis - bicyclo[3.3.0]*octan - 3 - ethylene - ketal* **18**

To a soln of freshly distilled oxalylchloride (1.43 ml, 2.075 g, 16.3 mmol) in dry CH_2Cl_2 (50 ml) at −50° was added dry DMSO (2.7 ml) dropwise, followed by a soln of **17** (693 mg, 3.27 mmol) in CH_2Cl_2 (5 ml). After stirring at −50° for 30 min dry Et_3N (5.4 ml) was added, and the mixture warmed to 20°. Sat $NaHCO_3$ aq (50 ml) was added, the CH_2Cl_2 layer was separated, and the aqueous layer further extracted with CH_2Cl_2 (2 × 50 ml). The combined extracts were washed with sat NaCl aq (10 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed over florisil eluting with Et_2O/petrol to give **18** (459 mg, 67%). IR ($CHCl_3$) 1732 cm^{-1}. NMR (90 MHz) $CDCl_3$ δ 1.06 (3H, s), 1.07 (3H, s), 1.52–1.80 (2H, m), 1.90–2.28 (4H, m), 2.70–3.02 (2H, m), 3.87 (4H, m). This material was used directly in the reduction experiments.

Reduction of **18**

(i) *With* $LiAlH_4$. Treatment of **18** (90 mg) with $LiAlH_4$ (17 mg) in dry THF (5 ml) in the usual way gave **17/19** (2:1). The ratio was determined by a comparison of the intensity of one set of Me peaks in the NMR spectrum: δ 0.99 for **17**, δ 1.05 for **18**.

(ii) *With* $NaBH_4$. Treatment of **18** (89 mg) with $NaBH_4$ (80 mg) in EtOH (5 ml) gave **17/19** (6:5).

(iii) *With* $LiAl(OBu^t)_3H$. Treatment of **18** (95 mg) with $LiAl(OBu^t)_3H$ (large excess) gave **17/19** (2:3).

(iv) *With* Li/NH_3. Treatment of **18** (77 mg) with Li (25 mg)/NH_3 (20 ml) gave **17/19** (9:1) **19** has R_f 0.40 (1:3 EtOAc/petrol).

1 - Methyl - 3 - (dimethyl - t - butylsilyloxy) - 4,4 - dimethyl - hept - 6 - en - 1 - yne **21**

To a soln of **12** (9.2 g) in THF (100 ml) was added benzyltriethylammonium chloride (20.7 g) followed by KF · $2H_2O$ (7.7 g), and the suspension heated at reflux for 3 hr, cooled to 20° and poured into water (250 ml). After extraction with Et_2O (3 × 150 ml), the combined extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was passed through a short florisil column, eluting with petrol, and purified by distillation under reduced pressure to give the terminal acetylene adduct (6.5 g, 90%), b.p. 61–63°/0.65 mm Hg. IR ($CHCl_3$) 3310, 1640 cm^{-1}. NMR (90 MHz) $CDCl_3$ δ 0.06 (3H, s), 0.12 (3H, s), 0.86 (15H, bs), 2.08 (2H, d, J = 7 Hz), 2.31 (1H, d, J = 2 Hz), 3.99 (1H, d, J = 2 Hz), 4.86–5.15 (2H, m), 5.56–6.08 (1H, m).

To a soln of the terminal acetylene (6.5 g, 25.8 mmol) in dry THF (100 ml) at −70° was added a 1.55 M soln of n-BuLi in hexane (20 ml, 31.0 mmol). After 15 min at −70° a soln of freshly distilled and dried MeI (8 ml, 18.32 g, 129 mmol) in THF (10 ml) was added dropwise, and the soln warmed to 20° over several hr. The above mixture was quenched with water (200 ml) and extracted with Et_2O (3 × 200 ml). The combined extracts were washed with sat NaCl aq (50 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was passed through a short column of florisil eluting with petrol, and bulb-to-bulb distillation gave **21** (6.7 g, 98%) (oven temp 90°/0.4 mm Hg). IR ($CHCl_3$) 22.15 and 1630 cm^{-1}. NMR (90 MHz) $CDCl_3$ δ 0.05 (3H, s), 0.11 (3H, s), 0.87 (15H, s), 1.79 (3H, d, J = 2 Hz), 2.05 (2H, d, J = 7 Hz), 3.98 (1H, q, J = 2 Hz), 4.88–5.16 (2H, m), 5.58–6.11 (1H, m). (Found: C, 72.36; H, 11.49. $C_{16}H_{30}OSi$ requires: C, 72.11; H, 11.35%.)

2 - Methyl - 5αH - 7,7 - dimethyl - 8α - (dimethyl - t - butylsilyloxy) bicyclo[3.3.0]*oct - 2 - en - 3 - one* **22** *and its 5βH-epimer* **23**

Treatment of **21** (6.00 g, 22.6 mmol) with $Co_2(CO)_8$ (7.80 g, 22.8 mmol) in heptane (60 ml) at 110° for 20 hr using the general procedure described before, gave after chromatography and bulb-to-bulb distillation **22** (3.34 g, 50%) (oven temp 120°/1 mm Hg), **22** has— IR ($CHCl_3$) 1701 and 1668 cm^{-1}. NMR (220 MHz) $CDCl_3$ δ −0.05 (3H, s), 0.04 (3H, s), 0.73 (3H, s), 0.79 (9H, s), 0.97 (1H, dd, J = 13 and 7 Hz), 1.05 (3H, s), 1.68 (3H, d, J = 2 Hz), 1.86–2.01 (2H, m), 2.65 (1H, dd, J = 19 and 6 Hz), 3.09–3.26 (1H, m), 4.03 (1H, s), **23** has—IR ($CHCl_3$) 1702 and 1665 cm^{-1}. NMR (220 MHz) $CDCl_3$ δ −0.01 (6H, s), 0.71 (3H, s), 0.82 (9H, s), 1.03 (3H, s), 1.13 (1H, dd, J = 13 and 8 Hz), 1.71 (3H, d, J = 1 Hz), 2.77–1.93 (2H, m), 2.53 (1H, dd, J = 18 and 7 Hz), 2.60–2.80 (1H, m), 4.47 (1H, s). Satisfactory combustion analysis was obtained on the dihydro-derivative of **22**.

2,7,7 - Trimethyl - 8α - (dimethyl - t - butylsilyloxy) - cis - bicyclo[3.3.0]*octan - 3 - one* **24**

To a soln of **22** (3.34 g, 11.4 mmol) in 95% EtOH (50 ml) containing 10% Pd/C (200 mg) was stirred at 20° under H_2 (balloon) for 20 hr. The mixture was filtered through celite, washed with EtOH, and chromatographed over florisil eluting with Et_2O/petrol to give **24** (3.09 g, 92%) as a 4:1 mixture of epimers at C-2. IR ($CHCl_3$) 1730 cm^{-1}. (Found: C, 68.16; H, 10.36. $C_{17}H_{32}O_2Si$ requires: C, 68.86; H, 10.88%.)

2β,7,7 - Trimethyl - 8α - (dimethyl - t - butylsilyloxy) - 2 - allyl - cis - bicyclo[3.3.0]*octan - 3 - one* **25**

To a suspension of NaH (530 mg, 59.3% dispersion in oil, 13.1 mmol) in dry DME (100 ml) was added a soln of **24** (3.04 g, 10.4 mmol) in dry DME (5 ml). The mixture was heated at 70° for 2 hr and freshly distilled allylbromide (11.5 ml; 16.08 g, 133 mmol) added in one portion. After 0.5 hr at 70° the mixture was cooled to 20° and solid NH_4Cl (3 g), followed by water (5 ml) added. The solvent was removed *in vacuo*, and the residue partitioned between water (100 ml) and Et_2O (100 ml). The Et_2O layer was separated, and the aqueous layer extracted with Et_2O (2 × 100 ml). The combined extracts were washed with sat NaCl aq (50 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the residue over florisil eluting with Et_2O/petrol (1:3) to give **25** (2.76 g, 79%). IR ($CHCl_3$) 1740 and 1635 cm^{-1}. NMR (220 MHz) $CDCl_3$ δ −0.02 (3H, s), 0.00 (3H, s), 0.79 (9H, s), 0.82 (3H, s), 0.87 (3H, s), 0.9–1.1 (1H, m), 3.55 (1H, d, J = 7.5 Hz), 4.86–5.00 (2H, m), 5.45–5.67 (1H, m). This material was used directly in the Wacker oxidation step.

2β,7,7 - Trimethyl - 8α - (dimethyl - t - butylsilyloxy) - 2α - acetonyl - cis - bicyclo[3.3.0]*octan - 3 - one* **26**

O_2 was bubbled through a mixture of $PdCl_2$ (300 mg) and CuCl (810 mg) in DMF (40 ml) and water (10 ml) for 2 hr. The allyl derivative **25** (1.50 g, 4.46 mmol) in DMF (5 ml) was added, and the mixture stirred at 20° for 24 hr with O_2 being bubbled through the mixture. The above soln was diluted with water (100 ml), and extracted with Et_2O (3 × 200 ml). The combined extracts were washed with sat $NaHCO_3$ aq (100 ml) and dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by chromatography over florisil eluting with Et_2O/petrol (1:3) to give **26** (1.0 g, 64%). IR ($CHCl_3$) 1727 and 1712 cm^{-1}. NMR (220 MHz) $CDCl_3$ δ −0.30 (3H, s), 0.00 (3H, s), 0.77 (12H, s), 0.86–1.07 (1H, m), 0.88 (3H, s), 0.90 (3H, s), 1.72–2.04 (2H, m), 1.92 (3H, s), 2.32 (1H, dd, J = 11 and 7 Hz), 2.50–2.80 (2H, m), 2.69 (1H, d, J = 19 Hz), 2.87 (1H, d, J = 19 Hz), 3.67 (1H, d, J = 8 Hz). (Found: C, 68.16; H, 10.18. $C_{20}H_{36}O_3Si$ requires: C, 68.18; H, 10.23%.)

(3aβ,3bα,4β,6aα) - 3a,3b,4,5,6,6a,7 - Octahydro - 3,3a,5,5 - tetramethyl - 4α - (dimethyl - t - butylsilyloxy) - cyclopenta[4,5]*pentalene - 2 - one* **27**

To a soln of **26** (1.75 g, 4.97 mmol) in dry t-BuOH (20 ml) was added a complex of t-BuOK/t-BuOH (1:1 ratio, 465 mg) in one portion. After 10 min at 20° solid NH_4Cl (530 mg) was

added and the mixture evaporated *in vacuo*. The residue was partitioned between H_2O (50 ml) and Et_2O (100 ml), the organic layer separated, and the aqueous layer extracted with Et_2O (2 × 100 ml). The combined extracts were washed with sat NaCl aq (50 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed over florisil eluting with Et_2O/petrol (1:3) to give **27** (1.23 g, 74%). IR ($CHCl_3$) 1695 and 1632 cm^{-1}. NMR (220 MHz) $CDCl_3$ δ −0.02 (3H, s), 0.00 (3H, s), 0.79 (9H, s), 0.83 (3H, s), 0.93 (3H, s), 1.11 (3H, s), 1.07–1.21 (1H, m), 1.76 (1H, dd, J = 13 and 7 Hz), 2.04–2.24 (2H, m), 2.27 (2H, s), 2.60–2.79 (2H, m), 3.73 (1H, d, J = 7.5 Hz), 5.60 (1H, s). (Found: C, 71.52; H, 10.01%. $C_{20}H_{34}O_2Si$ requires: C, 71.86; H, 10.18.)

(3aβ,3bα,4β,6aα,7α) - 3a,3b,4,5,6,6a,7 - *Octahydro* - 3,3a,5,5 - *tetramethyl* - 4α,7 - *dihydroxycyclopenta*[4,5]*pentalene* - 2 - *one* **32**

To a soln of t-BuOK/t-BuOH (1:1 ratio, 4.76 g) in dry DME (100 ml) was added **27** (850 mg) in DME (10 ml). After 2 hr at 20° the mixture was quenched with AcOH/H_2O (1:1, 25 ml), and partitioned between Et_2O (100 ml) and sat $NaHCO_3$ aq (300 ml). The organic layer was separated, dried ($MgSO_4$), and concentrated *in vacuo* to give **28**, which was used directly in the subsequent stages.

To a soln of MCPBA (80% pure, 550 mg, 2.55 mmol) in dry CH_2Cl_2 (40 ml) was added a soln of **28** (crude from previous step) in CH_2Cl_2 (10 ml). After 1 hr at 20° the mixture was diluted with Et_2O (200 ml), washed with sat $NaHCO_3$ aq (2 × 25 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was filtered through a short florisil column eluting with Et_2O/petrol (1:1) to give the crude **29**, which was dissolved in dry CH_2Cl_2 (25 ml) and treated with DBU (0.5 ml). After 15 min at 20° CH_2Cl_2 (75 ml) was added and the soln washed with 1 N HCl (20 ml), dried (Na_2SO_4), and evaporated *in vacuo*. Chromatography of the residue on florisil eluting with EtOAc/petrol (1:1) gave **30** (306 mg, 34% from **27**), m.p. 110–125°. IR ($CHCl_3$) 3600, 3400, 1700 and 1635 cm^{-1}. NMR (220 MHz) $CDCl_3$ δ 0.01 (3H, s), 0.04 (3H, s), 0.81 (9H, s), 0.87 (3H, s), 1.02 (3H, s), 1.31–1.42 (1H, m), 1.35 (3H, s), 1.74 (1H, t, J = 12 Hz), 2.09 (1H, dd, J = 12 and 7.5 Hz), 2.32–2.42 (2H, m), 2.68–2.88 (1H, m), 3.77 (1H, d, J = 7.5 Hz), 4.65 (1H, dd, J = 7 and 2 Hz), 5.78 (1H, s).

To a soln of **30** (260 mg, 0.74 mmol) in dry THF (20 ml) was added pyridinium polyhydrogen fluoride (3 ml), and the mixture stirred at 60° for 8 hr. After cooling to 20° the mixture was poured onto ice-water (50 ml) and extracted with $CHCl_3$ (2 × 75 ml). The extracts were washed with water (50 ml), 10% $NaHCO_3$ aq (50 ml), sat NaCl aq (50 ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed over florisil eluting with EtOAc/petrol (1:1) to give **32** (129 mg, 74%), m.p. 156–158° (lit.[4] 156–158°) from Et_2O/hexane. IR ($CHCl_3$) 3610, 3420, 1702 and 1632 cm^{-1}. NMR (220 MHz) $CDCl_3$ δ 0.93 (3H, s), 1.09 (3H, s), 1.41–1.55 (1H, m), 1.43 (3H, s), 1.85 (1H, dd, J = 13 and 10 Hz), 1.95 (1H, bs), 2.21 (1H, dd, J = 12 and 9 Hz), 2.37 (1H, d, J = 17 Hz), 2.50 (1H, d, J = 17 Hz), 2.62–2.83 (1H, m), 2.66 (1H, bs), 3.81 (1H, d, J = 8 Hz), 4.65 (1H, d, J = 5 Hz), 5.83 (1H, s). This was identical with an authentic sample kindly provided by Professor B. M. Trost.

1 - *Trimethylsilyl* - 4 - *ethoxycarbonyl* - 4 - *methyl* - *hept* - 6 - *en* - 1 - *yne* **45**

To a soln of diisopropylamine (15.42 ml, 0.11 mol) in dry THF (100 ml) under argon at −70° was added n-BuLi (68.75 ml, 1.6 M soln in hexane 0.11 mol). Diethylmethylmalonate (17.2 ml, 0.10 mol) in THF (90 ml) was added to the above soln, and the resulting mixture warmed to 0° over 1 hr. Allyl bromide (17.31 ml, 0.20 mol) in THF (10 ml) was added dropwise to the diethylmethylmalonate anion soln at 0°, and the mixture warmed to 20° and held at this temp for 1.5 hr. The mixture was quenched with NH_4Cl aq (200 ml), extracted with Et_2O (2 × 100 ml), washed with sat NaCl aq, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was distilled to give **42** (21.2 g, 99%). B.p. 74°/0.8 mm.[14]

A soln of **42** (5.36 g, 25 mmol), water (0.9 ml, 50 mmol), anhyd LiI (5.26 g, 37.9 mmol) and dry DMSO (25 ml) was heated to 2.60 (1H, dd, J = 17.5 and 6.5 Hz), 3.17–3.06 (1H, m), 3.21 (1H, d, J = 18.8 Hz), 4.16 (2H, q, J = 7.1 Hz). (Found: C, 64.15; H, 8.80; Si, 9.86%. $C_{15}H_{24}O_3Si$ requires: C, 64.24; H, 8.63; Si, 10.01.)

7 - *Methyl* - 7 - *carboxy* - 5α/5β - *bicyclo*[3.3.0]*oct* - 2 - *en* - 3 - *one* **48/49**

A mixture of esters **46/47** (0.89 g, 3.17 mmol) dissolved in 35% methanesulfonic acid (35 ml) was heated at 75° for 2.25 hr. The cooled mixture was diluted with water (100 ml) and extracted with EtOAc (2 × 50 ml). The extract was dried ($MgSO_4$) and evaporated *in vacuo* to give **48/49** (0.55 g, 96%) as a 1.34:1 mixture of epimers, separated by chromatography over silica gel, eluting with 1:1:2 EtOAc/Et_2O/petrol and 1% AcOH, **48**, m.p. 79–80°. IR ($CHCl_3$) 3200–2790, 1725, 1702 and 1635 cm^{-1}. NMR (360 MHz) δ 1.18 (1H, t, J = 12.6 Hz), 1.41 (3H, s), 2.12–2.06 (1H, m), 2.50 (1H, d, J = 18.5 Hz), 2.63 (1H, dd, J = 18.0 and 6.3 Hz), 2.72 (1H, dd, J = 7.7 and 12.6 Hz), 3.18–3.16 (1H, m), 3.39 (1H, d, J = 18.5 Hz), 5.94 (1H, s). (Found: C, 66.83; H, 6.79%. $C_{10}H_{12}O_3$ requires: C, 66.65; H, 6.71.) *Compound* **49**, NMR (360 MHz) δ 1.50 (3H, s), 1.76 (1H, t, J = 12.4 Hz), 2.17–2.11 (2H, m), 2.53 (1H, d, J = 18.6 Hz), 2.66 (1H, dd, J = 18.0 and 6.2 Hz), 3.21–3.18 (1H, m), 3.25 (1H, d, J = 18.6 Hz), 5.92 (1H, s), m.p. 89.5–92°.

Equilibration of **48/49**. A soln of **48/49** (1.34:1, 26 mg), *p*-TsOH · H_2O (13 mg) in benzene (1 ml) was heated at reflux for 4 hr. Work-up gave **48/49** (1.68:1, 26 mg).

7 - *Methyl* - 7 - *carboxymethyl* - cis - *bicyclo*[3.3.0]*octan* - 3 - *one* **51/52**

A soln of **48/49** (30 mg, 0.17 mmol) in EtOAc (1.5 ml) was hydrogenated over 10% Pd/C at 35° for 2 hr. Filtration and evaporation gave **38/50** (100%). The mixture of acids (80 mg from combined runs) was converted into their respective methyl esters by treatment with diazomethane, and separated by chromatography over silica gel eluting with 30% EtOAc/petrol. *Compound* **51**, IR ($CHCl_3$) 3045–2840 and 1730 cm^{-1}. NMR (360 MHz) δ 1.27 (2H, dd, J = 13.6 and 7.8 Hz), 1.33 (3H, s), 2.04 (2H, dd, J = 3.9 and 19.3 Hz), 2.50 (2H, ddd, J = 1.80, 9.7 and 19.3 Hz), 2.61 (2H, dd, J = 7.8 and 13.6 Hz), 2.86–2.73 (2H, m), 3.68 (2H, s). (Found: C, 66.89; H, 7.85%. $C_{11}H_{16}O_3$ requires: C, 67.32; H, 8.22.) *Compound* **52**, NMR (360 MHz) δ 1.28 (3H, s), 1.96, 180° and maintained at this temp for 24 hr. The mixture was cooled, poured into water and extracted with petrol (2 × 100 ml). The extract was washed with brine, dried ($MgSO_4$), and distilled. The residue was distilled under vacuum to give **43** (2.56 g, 72%). B.p. 99°/aspirator vacuum, and recovered **42** (0.76 g, 14%).

To a soln of diisopropylamine (5.49 g) in THF (40 ml) under argon at −70° was added BuLi (24.5 ml of a 1.6 M soln in hexane). After 40 min a soln of **43** (4.65 g) in THF (5 ml) was added, the mixture was warmed to 0° over 1 hr and a soln of **44** (6.84 g) in THF (5 ml) added dropwise. After 4 hr at 20° the mixture was quenched with sat NH_4Cl aq (100 ml) and extracted with Et_2O (2 × 100 ml). The extract was washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was chromatographed over silica gel eluting with 5% Et_2O/petrol to give **45** (2.94 g, 71%) (29% recovered **43**). B.p. 66°/10 mm. IR ($CHCl_3$) 3067–2800, 2087, 1724, 1643 and 840 cm^{-1}. NMR (90 MHz) $CDCl_3$ δ 0.13 (9H, s), 1.24 (3H, s), 1.25 (3H, t, J = 7.1 Hz), 2.42–2.30 (2H, m), 2.46 (2H, s), 4.15 (2H, q, J = 7.1 Hz), 5.11–5.05 (2H, m), 5.73–5.63 (1H, m). (Found: C, 66.67; H, 9.65; Si, 10.90%. $C_{14}H_{24}O_2Si$ requires: C, 66.61; H, 9.58; Si, 11.13.)

2 - *Trimethylsilyl* - 7 - *methyl* - 7 - *ethoxycarbonyl* - 5α/β - *bicyclo*[3.3.0]*oct* - 2 - *en* - 3 - *one* **46/47**

In a resealable tube, heptane (60 ml) was purged with CO for 1 hr, and **45** (2.445 g, 9.69 mmol) and $Co_2(CO)_8$ (3.97 g, 11.61 mmol) were added. The soln was purged with CO for a further 1 hr, sealed and heated at 120° (oil bath) for 25 hr. Work-up as usual gave **46/47** (2.342 g, 86% 55:45 ratio), followed by separation by flash chromatography eluting with 1:1:4

Et_2O/EtOAc/petrol. IR ($CHCl_3$) 3030–2800, 1720, 1680, 1610, 1305, 838 and 860 cm^{-1}. NMR (360 MHz) **46** δ 0.185 (9H, s), 1.09 (1H, t, J = 12.5 Hz), 1.28 (3H, t, J = 7.1 Hz), 1.36 (3H, s), 2.00 (1H, dd, J = 17.5 and 3.9 Hz), 2.43 (1H, d, J = 18.6 Hz), 2.54 (1H, dd, J = 17.5 and 6.7 Hz), 2.64 (1H, dd, J = 12.5 and 7.8 Hz), 3.06–2.98 (1H, m), 3.37 (1H, d, J = 18.6 Hz), 4.17 (2H, q, J = 7.1 Hz), **47**, 0.19 (9H, s), 1.27 (3H, t, J = 7.1 Hz), 1.46 (3H, s), 1.66 (1H, t, J = 12.6 Hz), 2.12–2.05 (2H, m), 2.52 (1H, d, J = 18.8 Hz), (4H, d, J = 6.7 Hz), 2.13 (2H, dd, J = 4.1 and 19.4 Hz), 2.49 (2H, dd, J = 9.5 and 19.4 Hz), 2.90–2.83 (2H, m), 3.67 (3H, s).

1 - *Trimethylsilyl - propargyl methanesulfonate* **44**

To a soln of propargyl alcohol (2.04 ml, 35 mmol) in Et_2O (70 ml) under argon at −70° was added n-BuLi (27.22 ml, 2.7 M soln in hexane, 73.5 mmol). The mixture was stirred at −70° for 0.5 hr, warmed for 15 min, then re-cooled to −70° for 0.5 hr, followed by the addition of a soln of chlorotrimethylsilane (9.77 ml, 77 mmol) in Et_2O (10 ml). The resulting mixture was stirred at −70° for 1 hr, then at 20° for 2.5 hr and then quenched with H_2O (100 ml), extracted with Et_2O (2 × 50 ml), dried ($MgSO_4$), and distilled. The residue was treated with 1 N HCl (35 ml) at 20° for 2 hr. The mixture was saturated with NaCl and extracted with Rt_2O (2 × 50 ml), washed with brine, dried (Na_2SO_4), and distilled to give 1-trimethylsilyl propargyl alcohol in quantitative yield, b.p. 111°/aspirator.

To a soln of the alcohol (5.412 g, 50 mmol) in CH_2Cl_2 (50 ml) under argon at 0° was added Et_3N (7.67 ml, 55 mmol). After stirring for 10 min, to this resulting soln was added a soln of methanesulfonyl chloride (4.64 ml, 60 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred at 0° for 2 hr then quenched with brine containing 20 ml of 3 N HCl, extracted with Et_2O (2 × 25 ml), washed with $NaHCO_3$ aq, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed to yield **44** (6.81 g, 73%), as a low melting solid (*ca* 0°), stable if stored in a freezer.

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