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A Regio- and Stereocontrolled Synthesis of (+)-Isocarbacyclin via (1S,2R,5R)-Bicyclo[3.3.0]oct-6-en-endo-2-ol

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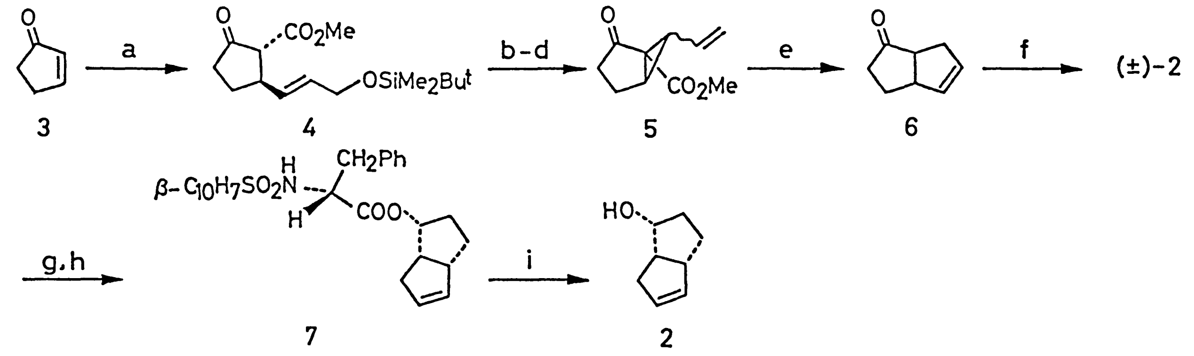
An expeditious synthesis of (+)-isocarbacyclin based on a facile access to (1S,2R,5R)-bicyclo[3.3.0]oct-6-en-endo-2-ol has been accomplished, incorporating controlled ene-reaction and elaboration of ω appendage via Julia coupling as key steps.

The growing therapeutic potential of (+)-isocarbacyclin (**1**)$^{1)}$ for cardiovascular and circulatory disorders has sparked considerable interest in new and imaginative strategies toward its practical synthesis.$^{2-4)}$ Following the initial syntheses involving annulation of a five-membered ring onto cyclopentane derivatives elaborated from a "Corey lactone",$^{2)}$ much attention has recently been focused on the approaches via the double vicinal C-C coupling process originating with (R)-4-hydroxy-2-cyclopentenone.$^{3)}$ Independent of these strategies, our own efforts centered on the development of the expeditious synthetic methods for chiral bicyclo[3.3.0]octane derivatives suitably functionalized for the controlled assembly of **1**. We have recently developed a convergent synthesis of **1** based on novel methods for linking α and ω appendages to a chiral bicyclo[3.3.0]octane nucleus readily constructed by employing rhodium(II)-catalyzed intramolecular C-H insertion.$^{5,6)}$ Along this line, we wish to report herein an alternative synthesis of **1** via (1S,2R,5R)-bicyclo[3.3.0]oct-6-en-endo-2-ol (**2**) readily obtainable through resolution of its racemate prepared by an improved method, wherein the key steps involve a regio- and stereocontrolled ene reaction and a stereocontrolled elaboration of ω appendage via Julia coupling.$^{7)}$

The access to the chiral building block **2** was implemented as detailed in Scheme 1. While we previously described a high-yield route to bicyclo[3.3.0]oct-6-en-2-one (**6**) incorporating lithium iodide-promoted vinylcyclopropane-cyclopentene rearrangement as a key step,$^{8)}$ one disadvantage for the large-scale preparation was a use of expensive and toxic phenylselenenyl chloride for the preparation of the starting methyl 2-oxo-1-cyclopentenecarboxylate. This problem was now overcome by the device of a conjugate addition/C-methoxycarbonylation sequence on 2-cyclopentenone (**3**). Thus, conjugate addition of the higher order cuprate$^{9)}$ derived from 3-(tert-butyldimethylsiloxy)-1-lithio-1-propene (E:Z=88:12) to **3** followed by trapping of the intermediate enolate with methyl cyanoformate$^{10)}$ led to the one-pot formation of the 2,3-trans-β-keto ester **4** with exclusive E stereochemistry (82% yield), which was uneventfully



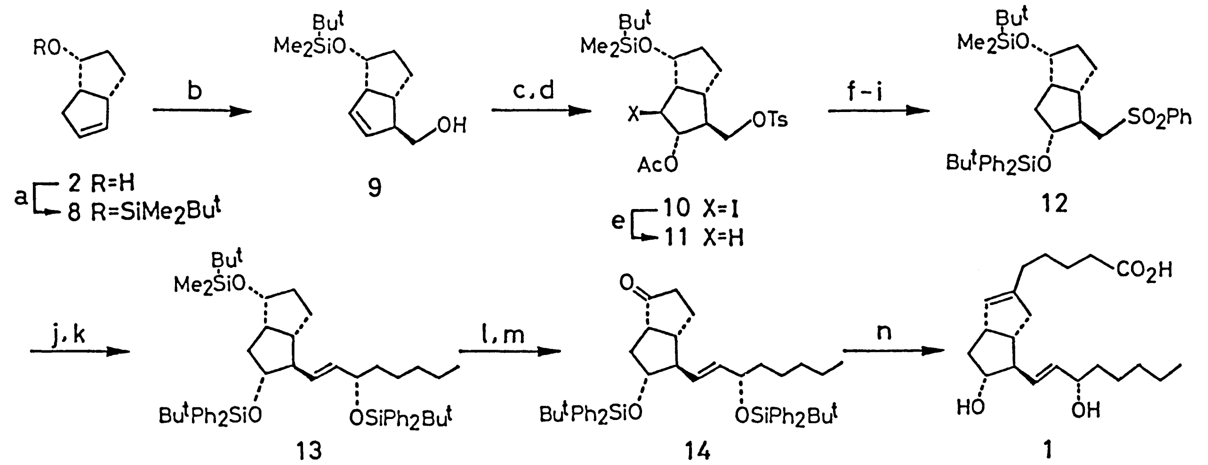
(a) $(t\text{-BuMe}_2\text{SiOCH}_2\text{CH=CH})_2\text{Cu(CN)Li}_2$ (1.5 equiv.), THF, -78 °C, 10 min; NCCO_2Me (1.5 equiv.), HMPA (1.8 equiv.), -78 °C, 10 min, 82%. (b) 10% aq.HCl-THF (1:10), 91%. (c) PhOCOCl, pyridine, benzene, 0.5 h, 90%. (d) $\text{Pd(PPh}_3)_4$ (3 mol%), PPh_3 (3 mol%), THF, sealed tube, 10 °C, 3 h, 78%. (e) LiI (2 equiv.), DMF, 110 °C, 3 h, then 135 °C, 4.5 h, 71%. (f) LiAlH_4, ether, -78 °C, 0.5 h, 87%. (g) N-(2-naphthalenesulfonyl)-(R)-phenylalanyl chloride (1.35 equiv.), pyridine (1.8 equiv.), THF, 20 °C, 0.5 h, 94%. (h) three recrystallization from EtOH-hexane (1:2), 32% (64% of theory). (i) 40% aq.KOH-MeOH (1:2), 60 °C, 3.5 h, 87%.

Scheme 1.

converted to **6** via the previously developed route.[8] This sequence can provide access to large quantities of **6** in five steps and 37% overall yield from **3**.

Reduction of **6** with LiAlH_4 led exclusively to the formation of (±)-endo-alcohol (±)-**2**, the resolution of which was then examined by using a variety of sulfonamides of a homochiral phenylalanyl chloride as resolving agents.[11] After much experimentation aiming at the resolution by recrystallization, N-(2-naphthalenesulfonyl)-(R)-phenylalanyl chloride[12] was found to be a superior choice. Thus, a mixture of the diastereomeric esters was cleanly separated by three recrystallization from ethanol-hexane (1:2) to give the ester **7**, mp 127.5-128.5 °C, $[\alpha]_D^{23}$ +11.8°(c 1.21, CHCl_3), as a single diastereomer in 32% yield (64% of theory). Alkaline hydrolysis of **7** furnished the desired (1S,2R,5R)-bicyclo[3.3.0]oct-6-en-endo-2-ol (**2**), $[\alpha]_D^{23}$ -71.2°(c 1.12, CHCl_3), the homochirality and absolute configuration of which were established by correlation with the known bicyclo[3.3.0]octan-2-one.[13]

With access to ample quantities of **2** secured, the stage was now set for the installation of C-11α (PG numbering) hydroxy group and the stereocontrolled elabolation of ω appendage (Scheme 2). While dimethylaluminum chloride-promoted ene reaction of cyclic olefins such as cyclopentene or cyclohexene with formaldehyde was reported to form a mixture of products,[14] the ene reaction with **8**, $[\alpha]_D^{23}$ -5.84°(c 1.49, CHCl_3), proceeded on the less hindered exo face to give the ene adduct **9**, $[\alpha]_D^{23}$ +194°(c 1.03, CHCl_3), in 52% yield (70% based on the recovered starting material), with no trace of its regioisomer. The noteworthy regiocontrol can be understood by considering the preferential abstraction of methylene hydrogen due to stereoelectronic effects on 1,5-hydrogen shift.[14] Tosylation of **9** was followed by a regio- and stereocontrolled iodoacetoxylation to furnish the iodo acetate **10**, $[\alpha]_D^{23}$ -21.1°(c 1.25, CHCl_3), in 79% yield, which on reductive deiodination with tri-n-butyltin hydride afforded the acetate **11**, $[\alpha]_D^{23}$ -9.59°(c 1.05, CHCl_3), in 96% yield. Displacement of **11** with potassium



(a) t-BuMe$_2$SiCl, imidazole, DMF, 1.5 h, 97%. (b) (HCHO)$_n$ (2 equiv.), 5.0 M Me$_2$AlCl in hexane (3 equiv.), CH$_2$Cl$_2$, -40 °C, 1.5 h, 52% (70% based on the recovered starting material). (c) TsCl, DMAP, pyridine, 40 °C, 2.5 h, 96%. (d) I$_2$ (1.1 equiv.), AgOAc (1.2 equiv.), AcOH, 1 h, 83%. (e) (n-Bu)$_3$SnH, benzene, 60 °C, 10 min, 96%. (f) PhSK, DMSO, 1 h, 94%. (g) MCPBA, CH$_2$Cl$_2$, -20 to 0 °C, 1.5 h, 93%. (h) K$_2$CO$_3$, MeOH, 2 h, 91%. (i) t-BuPh$_2$SiCl (1.2 equiv.), DMAP (2 equiv.), (i-Pr)$_2$NEt (0.2 equiv.), DMF, 60 °C, 5 h, 94%. (j) n-BuLi (1.05 equiv.), HMPA (3 equiv.), THF, -78 to -55 °C, 0.5 h; (S)-2-(t-butyldiphenylsiloxy)heptanal (1.1 equiv.), -78 °C, 0.5 h, 75%. (k) MsCl, DMAP, pyridine, 60 °C, 4.5 h; 10% Na-Hg, Na$_2$HPO$_4$, MeOH, -20 to 0 °C, 9.5 h, 72%. (l) PPTS (0.3 equiv.), EtOH, 45 °C, 16 h, 84%. (m) DMSO, (COCl)$_2$, CH$_2$Cl$_2$, -60 °C, 15 min; Et$_3$N, -60 to 0 °C, 0.5 h, 84%. (n) See Ref. 6.

Scheme 2.

thiophenoxide and subsequent oxidation with m-chloroperbenzoic acid followed by protective group interchange provided the sulfone **12**, $[\alpha]_D^{23}$ +4.29°(c 1.01, CHCl$_3$), in 75% yield. The coupling of the carbanion generated from **12** and n-butyllithium with (S)-2-(tert-butyldiphenylsiloxy)heptanal[15)] in THF in the presence of HMPA at -78 °C proceeded smoothly to produce the adduct as a diastereomeric mixture, which underwent mesylation and subsequent reductive elimination with sodium amalgam to give the olefin **13**, $[\alpha]_D^{23}$ -1.54°(c 1.11, CHCl$_3$), in 54% overall yield, with no detectable amount of the Z double bond isomer.[16)] Somewhat surprizingly, however, this coupling under Wicha's conditions[17)] with the aid of BF$_3$·Et$_2$O did not work. Selective removal of tert-butydimethylsilyl ether protection[18)] and subsequent Swern oxidation produced the ketone **14**, $[\alpha]_D^{23}$ +20.7°(c 0.99, CHCl$_3$), in 71% yield, which was transformed in a controlled manner to (+)-isocarbacyclin, $[\alpha]_D^{23}$ +8.8°(c 1.08, MeOH){lit.[6)] $[\alpha]_D^{23}$ +8.75°(c 0.72, MeOH)}, by a reported method.[6)]

In summary, we have demonstrated that (1S,2R,5R)-bicyclo[3.3.0]oct-6-en-endo-2-ol, now accessible in large quantities, can serve as a useful building block for (+)-isocarbacyclin synthesis. Studies directed toward the synthesis of its novel analogues for biological and pharmacological investigations are currently in progress in our laboratory.

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12) This reagent, mp 144-144.5 °C (dec.), $[\alpha]_D^{23}$ +3.43°(c 3.22, $CHCl_3$), was prepared from (R)-phenylalanine in 70% yield by the following operation: (1) 2-naphthalenesulfonyl chloride, aq.NaOH-ether, rt, 15 h; (2) PCl_5 (1.1 equiv.), benzene, 10 °C, 2.5 h.

13) The observed rotation, $[\alpha]_D^{23}$ +127°(c 2.95, $CHCl_3$), agreed well with the reported value for (1S,5S)-bicyclo[3.3.0]octan-2-one: $[\alpha]_D^{23}$ +126°(c 2.85, $CHCl_3$). J. K. Whitesell, M. A. Minton, and S. W. Felman, J. Org. Chem., 48, 2193 (1983).

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16) In stark contrast, the Julia coupling of the sulfone **12** with hexanal or benzaldehyde provided the corresponding olefins in E/Z ratios of 72:28 and 73:27, respectively.

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