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Studies on novel macrocyclization methods of cembrane-type diterpenoids: a Stille cyclization approach to (±)-isocembrene

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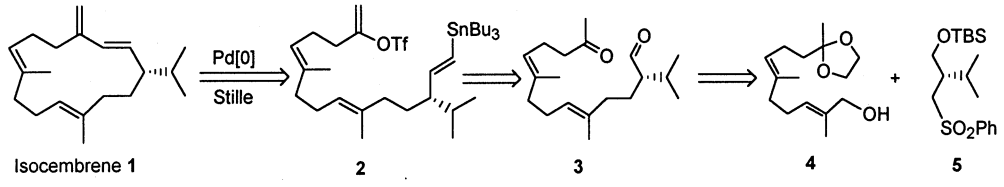
Abstract—An efficient total synthesis of (±)-isocembrene via an intramolecular Stille cross-coupling reaction is described. A novel strategy towards the 1,3-diene-based cembrane-type macrocyclic diterpenoids has been realized.

Cembranoids, a large family of diterpenoid natural products characterized by the presence of a 14-membered ring, have been isolated from various marine sources as well as some terrestrial organisms since the 1960s.[1] These diterpenoids have been of great interest to synthetic chemists and biologists because of their unusual structural features and remarkably wide range of biological activities.[1] Although a number of synthetic strategies for the construction of a 14-membered-ring system have appeared in the literature over the past three decades and notable progress has been made in this field, the lack of general method for the preparation of 14-membered rings presents an on-going challenge for total synthesis.[2] In continuation of our on-going project on the total synthesis and macrocyclization of cembrane-type diterpenoids, we describe herein an efficient macrocyclization methods which should be of general applicability in terpene synthesis. Intramolecular Pd-catalyzed cross coupling between an alkenylstannane and an alkenyl halide (or triflate) functionalities has now been firmly established as an important methodology for the construction of unsaturated heterocycles and carbocycles,[3] providing an attractive route for the assembly of a variety of cembrane-type compounds.[4]

Isocembrene **1**, a cembrane diterpenoid, was first isolated by Kashtanova and co-workers[5] in 1968 from *Pinus sibirica* and characterized spectroscopically and chemically as (1*S*,2*E*,7*E*,11*E*)-2,4(18),7,11-cembratetraene. Pattenden and Smithies accomplished the first total synthesis of (±)-**1** in 1996.[6] In continuation of our on-going project on the total synthesis and novel macrocyclization methods of cembrane diterpenoids, we have also completed a total synthesis of **1** using the Stille sp^2–sp^2 macrocyclization reaction as a key step to elaborate the stereodefined 1,3-diene unit in this compound. The synthetic strategy from the readily available *E*-geranyl acetone as outlined in Scheme 1 involves (1) chemoselective synthesis of *E*-alkenylstannanes from keto aldehydes **3** using Bu_3SnCHI_2 in DMF, (2) regioselective synthesis of vinyl triflate from a ketonic



Scheme 1. Retrosynthesis of isocembrene **1** based on intramolecular Pd-catalyzed Stille cross-coupling reaction.

Keywords: isocembrene; diterpenoids; cembranoids; Stille reaction.
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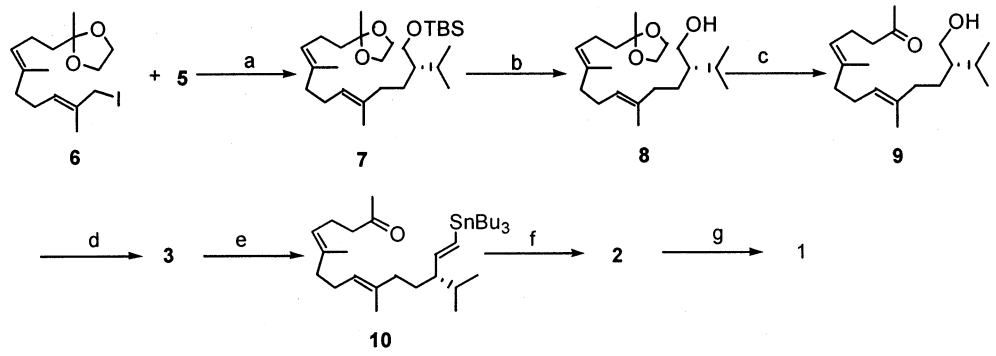

Scheme 2. *Reagents and conditions*: (a) 1. **5**+*n*-BuLi, THF, −40°C, 1.5 h, then **6**, −40°C to rt, 1.5 h, 89%; 2. Na (Hg), Na_2HPO_4, MeOH, rt, 16 h, 84%; (b) TBAF, THF, rt, 30 min, 95%; (c) *p*-TsOH, acetone, rt, 4 h, 95%; (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C to rt, 2 h, 92%; (e) Bu_3SnCHI_2, $CrCl_2$, DMF, rt, 5 h, 74%; (f) NaHMDS, $PhNTf_2$, THF, −78°C, 2 h, 84%; (g) $(Ph_3P)_4Pd$, LiCl, THF, reflux, 6 h, 76%.

carbonyl and (3) macrocyclization of precursor **2** containing the vinyl tin and vinyl triflate groups by an intramolecular Stille cross-coupling reaction.

Total synthesis of **1** is detailed in Scheme 2. Allylic alcohol **4**, readily available from geranyl acetone,[7] was converted into the corresponding iodide **6** by a standard method.[8] Coupling reaction of iodide **6** with the lithium salt of **5**[9] (formed by treatment with *n*-BuLi in THF at −40°C) in THF at −40°C proceeded smoothly to afford a coupling adduct, which was desulfonated to **7** by treatment with Na(Hg)[10] in MeOH. Desilylation of **7** with tetra-*n*-butylammonium fluoride in THF at rt gave the alcohol **8**, which was then treated with a catalytic amount of *p*-TsOH in acetone to give the keto alcohol **9**. After Swern oxidation, the keto aldehyde **3** was transformed[11] into *E*-alkenylstannane **10** by treatment with Bu_3SnCHI_2[12] in DMF in one step in good yield (74%); no methylenated material was observed in the crude ^1H NMR. Adding sodium hexamethyldisilazide (NaHMDS) rapidly to a diluted solution of vinyl tin **10** and *N*-phenyl triflimide[13] in excess (1.5–1.7 equiv.) at −78°C gave the triflate **2** containing only small amounts (<6% by 400 MHz ^1H NMR) of thermodynamic enolate in yield of 84%. Cyclization[14] of **2** was accomplished with tetrakis(triphenylphosphine) palladium (5 mol%) in the presence of lithium chloride (3 equiv.) under high dilution (10^{-3} M) in refluxing THF. Under these mild reaction conditions, no *E* to *Z* isomerization and no rearrangement of the exocyclic double bond occurred. Synthetic **1** showed identical spectral data with those of natural product **1** reported previously.[15]

In summary, an efficient and convergent total synthesis of (±)-isocembrene has been accomplished via an intramolecular Stille cross-coupling reaction. This protocol is expected to be applicable to the other cembrane-type diterpenoids.

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15. Selected spectral data. **2**, IR (film): 2957, 2927, 1601, 1472, 1072, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.78–0.91 (m, 21H, $Sn(CH_2CH_2CH_2CH_3)_3$ and $CH(Me)_2$), 1.22–1.29 (m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$), 1.39–1.66 (m, 7H, $Sn(CH_2CH_2CH_2CH_3)_3$ and $CH(Me)_2$), 1.90–2.00 (m, 8H, $4\times CH_2$), 2.20–2.28 (m, 2H, $CH_2C(OTf)=C$), 4.85 (d, $J=3.4$ Hz, 1H, *cis*-TfOC=CH*H*), 5.02 (d, $J=3.4$ Hz, 1H, *trans*-TfOC=C*H*H), 5.09–5.13 (m, 2H, 2×CH=C), 5.65 (dd, $J=18.9$, 8.7 Hz, 1H, C*H*=CHSn), 5.75 (d, $J=18.9$ Hz, 1H, =CHSn). Anal. calcd for $C_{33}H_{59}F_3O_3SSn$: C, 55.70; H, 8.36. Found: C, 55.35; H, 8.14.
1, IR (film): 2930, 2855, 1470, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.84 (d, $J=7.0$ Hz, 3H, Me), 0.89 (d, $J=7.0$ Hz, 3H, Me), 1.25–1.40 (m, 2H, $CH(Me)_2$ and $CHCHMe)_2$), 1.68 (s, 3H, CH=C*Me*), 1.70 (s, 3H, CH=C*Me*), 1.90–2.00 (m, 8H, $4\times CH_2$), 2.43–2.46 (m, 1H, C*H*HC=CHH), 4.85 (br s, 1H, C=CH*H*), 4.90 (br s, 1H, C=CH*H*), 5.09 (t, $J=7.0$ Hz, 1H, CH=C), 5.19 (t, $J=7.0$ Hz, 1H, CH=C), 5.50 (dd, $J=15.6$, 9.6 Hz, 1H, CH=C*H*CH), 5.94 (d, $J=15.6$ Hz, 1H, CH_2=CC*H*=CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 137.8, 135.8, 134.0, 132.3, 124.9, 123.8, 113.6, 50.0, 34.2, 33.0, 32.6, 32.2, 29.6, 28.4, 28.0, 24.0, 23.5, 20.7, 19.8; EIMS m/z: 272 (M^+, 5), 257 (M^+–Me, 12); HRMS (ESI): calcd for $C_{20}H_{32}$+H (M^++H) 273.2577, found 273.2571.