Synthesis of Hydrazulenes via Zr-Promoted Bicyclization of Enynes and Transition Metal-Catalyzed or Radical Cyclization of Alkenyl Iodides. Efficient Synthesis of (±)-7-*epi*-*β*-Bulnesene

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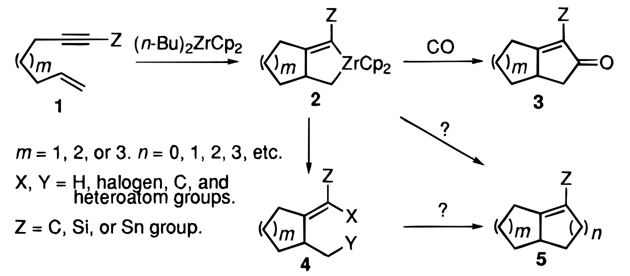
Bicyclization of enynes (**1**) and related π-compounds with zirconocene derivatives,[2] such as $(n\text{-Bu})_2ZrCp_2$,[3] has provided an efficient entry into fused ring systems as well as monocyclic compounds. In particular, the Zr-promoted bicyclization−carbonylation tandem[4] has served as an attractive alternative to the Co-based Pauson−Khand protocol.[5] In contrast with the latter, the Zr-based protocol is applicable to the bicyclization of dienes[6] (and diynes[3,7]) as well. Several complex natural products, such as pentalenic acid,[8] dendrobine,[9] and iridomyrmecin,[10] have been synthesized using the Zr-promoted bicyclization−carbonylation protocol. Another distinguishing feature of the Zr-based methodology is the fact that the bicyclization step producing metallacycles (**2**) can be performed in a discrete step. In principle, the metallacycles thus obtained can be converted into a variety of cyclic organic compounds, such as those represented by **4** and **5** (Scheme 1), via protonolysis,[2−4] halogenolysis,[2−4] and other reactions that organozirconiums can undergo.[11] However, these possibilities have not been adequately explored from the viewpoint of natural products synthesis. Thus, an application of the Zr-promoted bicyclization−protonolysis tandem to the synthesis of phorbol[12] appears to be the only reported example.

We report herein a few protocols for converting **2** into hydrazulenes involving (i) Pd-catalyzed cyclic carbometalation of alkenes,[13] (ii) Ni-catalyzed cyclic addition of alkenylchromiums to aldehydes,[14] and (iii) alkenyl radical cyclization reaction.[15] The synthetic utility and high efficiency of these procedures are demonstrated by the synthesis of (±)-7-*epi*-*β*-bulnesene (**6**)[16] in six steps in 16−24% overall yield from enyne **7**[10] via **8**−**12** (Scheme 2). The maximum ratio of 7-*epi*-*β*-bulnesene to *β*-bulnesene observed is about 90/10, and all transformations between **8** and **6** proceed with complete retention of stereochemistry. It is worth pointing out that the hydrazulene derivatives **11**−**13** having the *7R,*8S** configuration are potentially suitable intermediates for columellarin[17] (**14**) and other related terpenoids.

Scheme 1



With a general goal of developing a widely applicable methodology for the synthesis of hydrazulenes based on the Zr-promoted enyne bicyclization and a specific goal of devising an efficient route to a subgroup of hydrazulenes represented by **6** and **14**, enyne **7** was chosen as a test substrate, and its racemic mixture was prepared in four steps from (*E*)-crotyl alcohol via 3-methyl-4-penten-1-ol[18] and its iodo derivative,[19] the latter of which was cross-coupled with $LiC{\equiv}CCH_3$. The overall yield was 44%. The reaction of **7** with $(n\text{-Bu})_2ZrCp_2$ was performed as previously reported[10] except that the initially formed **8** was equilibrated at 50 °C for 5 h to give a 90/10 epimeric mixture in >90% combined yield by ^{1}H NMR.

Treatment of **8** with 2.3 equiv of ICl in CH_2Cl_2 (−78 °C, 1 h) and then warming to 23 °C over 2 h gave a 76% yield of **15**, which was converted to **16** in 86% yield by treatment with 2 equiv of dimethyl sodiomalonate in DMSO (50 °C, 10 h) and then to **17** in 91% yield by allylation with NaH and allyl bromide in DMF. As expected, the cyclic Heck reaction[13,20,21] of **17** using 5 mol % of $Pd(PPh_3)_4$ and NEt_3 (2 equiv) in refluxing MeCN for 10 h produced the *exo*-mode cyclization product **18** in 80% yield (Scheme 3).

Although the results shown in Scheme 3 were very favorable, **18** did not turn out to be a convenient intermediate for the synthesis of terpenoids such as **6** and **14**. Thus, for example, an attempt to excise its *exo*-methylene

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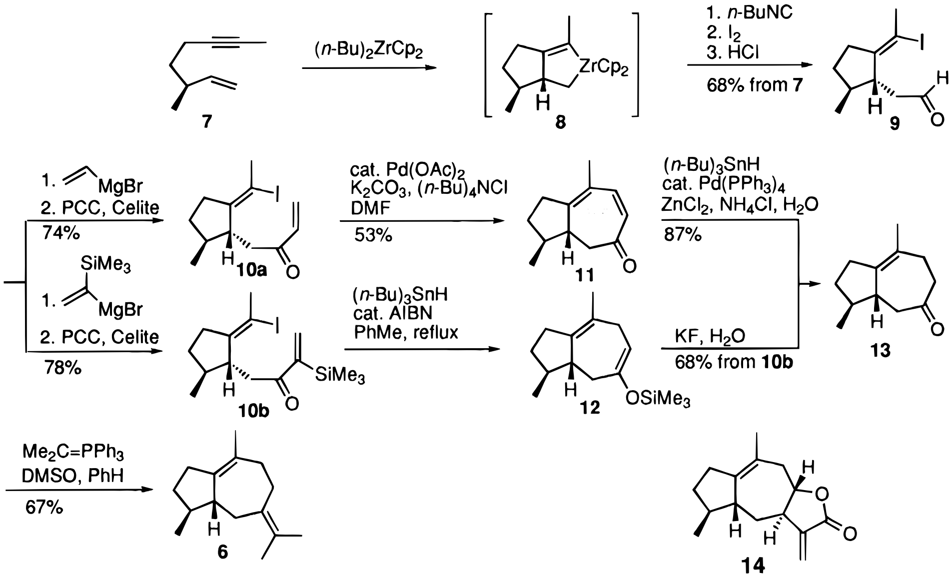
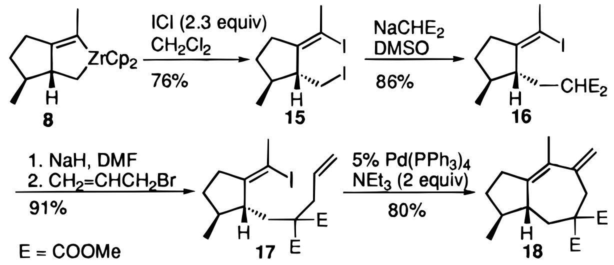
Scheme 2



Scheme 3



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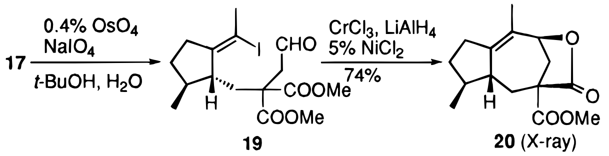

group with $NaIO_4$[22] in the presence of a catalytic amount of OsO_4 in a 1:1 mixture of *t*-BuOH and H_2O gave the corresponding 3-oxo derivative in only 10% yield. On the other hand, the same oxidation of **17** using 0.4 mol % of OsO_4 and 2.5 equiv of $NaIO_4$ afforded **19** in 54% yield. Its treatment with 4.3 equiv of $CrCl_2$ generated from $CrCl_3$ and $LiAlH_4$ in the presence of 5 mol % of $NiCl_2$ in DMF at 23 °C for 4 h[14] produced **20** as a stereoisomerically pure crystalline solid in 74% yield (Scheme 4). Its stereochemistry was established by X-ray crystallography. One potentially attractive feature of this cyclization reaction is that the two ester groups in **20** are stereospecifically differentiated for further synthetic elaborations.

For more efficient syntheses of simple hydrazulenes, such as **6**, we examined the feasibility of endo-mode cyclic carbopalladation. Although exo-mode cyclic carbopalladation is dominant,[13] we have previously observed the complete reversal of the mode of cyclic acylpalladation with the use of enones in the absence of phosphines.[23,24] Regiospecific conversion of **7** to **9** in 68% yield via sequential treatment with *n*-BuNC and I_2, as previously reported,[11] followed by vinylation and PCC oxidation in 74% combined yield, provided **10a** in 50% overall yield from **7**. Indeed, its treatment with 25 mol % of $Pd(OAc)_2$, 2.5 equiv of K_2CO_3, and 1 equiv of $(n\text{-Bu})_4NCl$ in DMF (100 mL per mmol of **10a**) at 23 °C for 12 h afforded a 90/10 mixture of **11** and its epimer in 53% combined yield (Scheme 2). Examination of the reaction mixture by NMR spectroscopy indicated the extent of *exo*-mode cyclization to be <3%, if any. No other monomeric product was detectable. So, the major side reaction must be a polymerization process. Conjugate reduction of **11** with $(n\text{-Bu})_3SnH$ (5 equiv), $ZnCl_2$ (8 equiv), NH_4Cl (2 equiv), and H_2O (3 equiv) in THF at 23 °C for 4 h[25] produced an 87% combined yield of a 90/10 mixture of **13** and its epimer, which was converted to a 90/10 mixture of (±)-7-*epi*-*β*-bulnesene (**6**) and (±)-*β*-bulnesene in 67% combined yield by treatment with $Me_2C{=}PPh_3$, as previously reported.[16]

Treatment of **10a** with $(n\text{-Bu})_3SnH$ (1.2 equiv) and 7 mol % of AIBN[15] in refluxing toluene for 1 d directly produced **13** in 30% yield, but the reaction was not clean. To alleviate these difficulties, **10b** containing a Me_3Si group was prepared and subjected to the same radical cyclization conditions. This reaction cleanly produced **12**, which was desilylated with aqueous KF to give **13** in 68% yield based on **10b** (Scheme 2). Interestingly, oxidation of **12** with *m*-chloroperbenzoic acid gave a 73% combined yield of a 60/40 mixture of two regioisomeric eight-membered lactones. It should also be parenthetically mentioned here that, although nonstereoselective, a higher yield of *β*-bulnesene can be attained by using **8** obtained under milder bicyclization conditions. The lowest ratio of **8** to its epimer observed is nearly 50/50.

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Supporting Information Available: Experimental procedures for the preparation of all isolated compounds and NMR spectra of **11**, **13**, and **6** as well as the ORTEP representation for **20** (14 pages).

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