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DIASTEREOSELECTIVE ZIRCONOCENE-PROMOTED BICYCLIZATION-CARBONYLATION OF ALLYLICALLY METHYL-SUBSTITUTED ENYNES. SYNTHESIS OF (+)-IRIDOMYRMECIN

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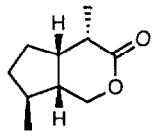
Summary: Allylically methyl-substituted 1,6-heptenynes, such as 3-methyl-1,6-octenyne, can be diastereoselectively converted to the corresponding bicyclic ketones, such as (5R,6S)-2,6-dimethylbicyclo[3.3.0]oct-1-en-3-one readily convertible to (+)-iridomyrmecin, the observed diastereomeric excesses of the bicyclization reaction being >90%.

It has recently been demonstrated that the zirconocene-promoted bicyclization of allylically hydroxy-substituted dienes[1] and enynes[2] can be diastereoselective and that the corresponding bicyclic ketones,[1a,2b] can be stereoselectively prepared.[3] In view of a large number of natural products containing nonpolar substituents, especially Me, in place of OH, such as iridomyrmecin[4] (**1**), silphiperfol-6-ene[5] (**2**) and pseudoivalin[6] (**3**), that are potentially accessible via the bicyclization-carbonylation sequence,[7] we decided to investigate the effects of a Me group in the allylic position of enynes on the stereochemistry of the zirconocene-promoted bicyclization. This study was also prompted by our recent finding that the course of the zirconocene-promoted alkyl-alkene and alkene-alkene coupling via zirconacyclopentane formation is strongly influenced by even small nonpolar substituents, such as Me.[8]



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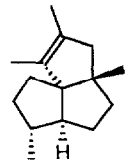

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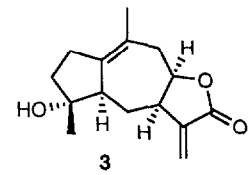
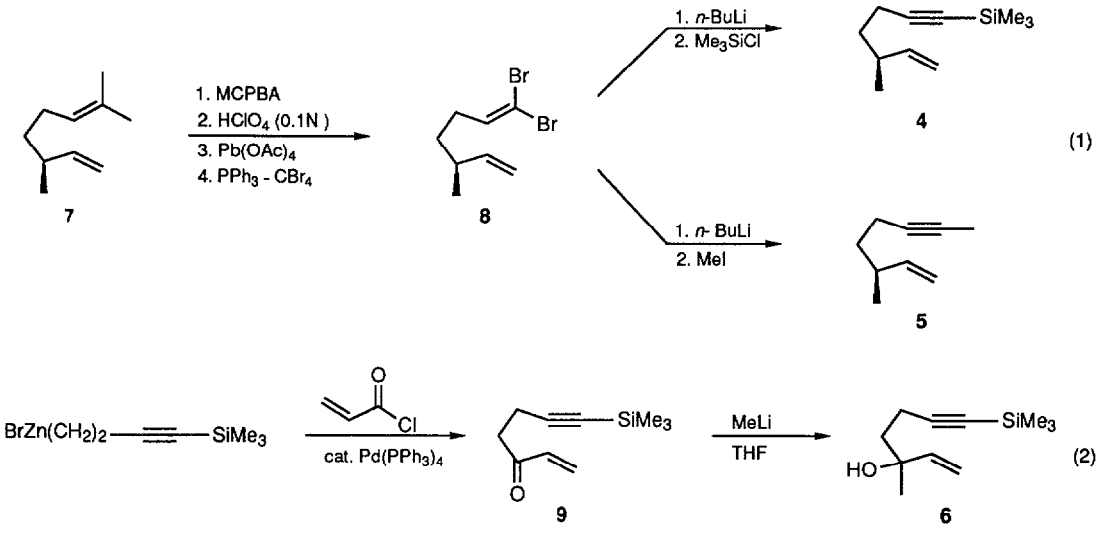


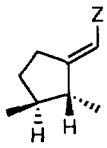
3

Three allylically Me-substituted 1,6-heptenynes **4-6** were prepared as follows. (+)-Citronellene (**7**), $[\alpha]_D^{20}$ +10 ± 1°, available from Fluka was converted in 46% yield to **8** via epoxidation with *m*-ClC_6H_4COOH, oxidation with $Pb(OAc)_4$,[9] and one carbon homologation with CBr_4 and PPh_3 in CH_2Cl_2 at 0 °C.[10] Treatment of **8** with *n*-BuLi (2.5 equiv) in THF followed by quenching with Me_3SiCl gave a 91% yield of **4**, while quenching with MeI provided **5** in 78% yield (eq. 1). The palladium-catalyzed reaction[11] of $Me_3SiC{\equiv}C(CH_2)_2ZnBr$[12] with acryloyl chloride gave **9** in 63% yield. Its reaction with MeLi afforded **6** in 72% yield (eq. 2).

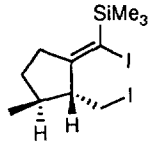


The enynes **4-6** were treated with a $ZrCp_2$ reagent generated in situ by the reaction of Cp_2ZrCl_2 with 2 equiv of *n*-BuLi.[7,13] Without isolation and/or characterization, the zirconabicyclic products were subjected to further reactions. Protonolysis (3N HCl), iodinolysis (I_2 in THF), and carbonylation followed by quenching with I_2[8] of the zirconabicycle derived from **4** produced **10a** (80%), **11** (55%), and **12a** (41%) in the yields indicated in parentheses. The diastereomeric excess in each case was >96% by ^{13}C NMR spectroscopy. Similarly, **5** was converted to **10b** (91%) and **12b** (73%) via protonolysis and carbonylation-iodinolysis, respectively. These reactions were >90% d.e. When the bicyclization reaction of **5** was carried out at 25 °C only for 3 h, protonolysis led to the formation of a 4:1 mixture of the two possible diastereomers. On the other hand, protonolysis after 18 h at 25 °C led to the >90% d.e. figure reported above. We judge that the reaction is reversible as previously indicated for a similar enyne[7] and that the fraction of the minor isomer under the kinetically controlled conditions is larger than that under the thermodynamically equilibrated conditions. If so, equilibration in the case of **4** must be considerably faster than that of **5**, since the >96% d.e. figure was obtained only after 3 h at 25°C. Quite unexpected was the >96% d.e. figure that the bicyclization reaction of **6** displayed. Protonolysis and carbonylation-iodinolysis of the bicyclization mixture gave **13** and **14** in 75 and 35% yields, respectively. Although the factors influencing the diastereochemistry of the reaction are not clear at this time, the predominant formation of the *exo*-OH isomer suggests that the OH group converted to a metallated derivative containing Li and/or Zr under the bicyclization conditions must exert a considerably greater steric demand than Me.

The stereochemical assignments of the bicyclic ketones are based on their ^1H NMR spectra including ^1H 2D NOESY NMR spectra. The identity of **12b**, $[\alpha]_D^{20}$ -78° (*c* 10.2, $CHCl_3$), was further confirmed by comparison of its spectra with those reported for its enantiomer, $[\alpha]_D^{20}$ +77.8° (*c* 9.42, $CHCl_3$), which has been prepared as an intermediate for the synthesis of **2**.[5b]



10 a : Z=$SiMe_3$
b : Z=Me



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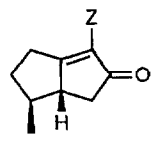
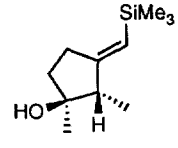


12 a : Z=$SiMe_3$
b : Z= Me



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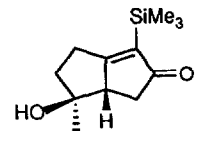
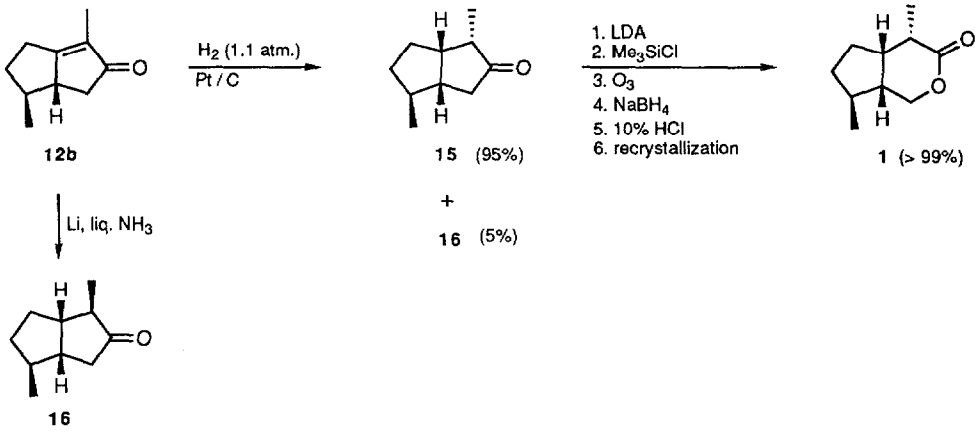


14

To demonstrate the applicability of the zirconocene-promoted bicyclization-carbonylation protocol to natural products synthesis, conversion of **12b** into (+)-iridomyrmecin[4] (**1**) was achieved as shown in Scheme I. Catalytic hydrogenation of **12b** (>98% d.e.) at 1.1 atm over 1% Pt/C in MeOH for 4 h at 25 °C gave **15** as a ~95% isomerically pure compound in 84% yield, the only isomer detectable by ^{13}C NMR spectroscopy being the 2-Me epimer (**16**). The use of Pd/C as a catalyst led only to a 3:1 mixture of **15** and **16**. An essentially 100% pure sample of **16** was readily obtainable via reduction of **12b** with Li in liquid NH_3. One-pot conversion of **15** into **1** was achieved as in Scheme I, following a sequence reported in the literature.[4b] After a short-path column chromatography (silica gel, 4:1 hexane/EtOAc), a 97:3 mixture of **1** and its epimer, i.e., isoiridomyrmecin, was obtained in 54% overall yield based on **15**. Recrystallization from hexane provided a 46% overall yield of a ≥99% pure sample of **1**:[4] mp 60.5-61.0 °C (lit.[4a] mp 60.5-61.0 °C); $[\alpha]_D^{23}$ +208° (lit.[4a] $[\alpha]_D$ +210°); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.95-1.25 (m, 2H), 1.06 (d, J = 6 Hz, 3H), 1.15 (d, J = 6.5 Hz, 3H), 1.7-1.9 (m, 4H), 2.5-2.8 (m, 2H), 4.17 (d, J = 12 Hz, 1H), 4.28 (dd, J = 12 and 3 Hz, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 12.76, 18.41, 29.89, 34.26, 37.38, 38.02, 41.27, 45.60, 68.13, 176.78; IR (Nujol) 1760 cm^{-1}.

Scheme I



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