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A NEW SYNTHETIC ROUTE TO JUVENILE HORMONE KINETIC RESOLUTION OF EPOXIDES USING ORGANOALUMINUM REAGENT

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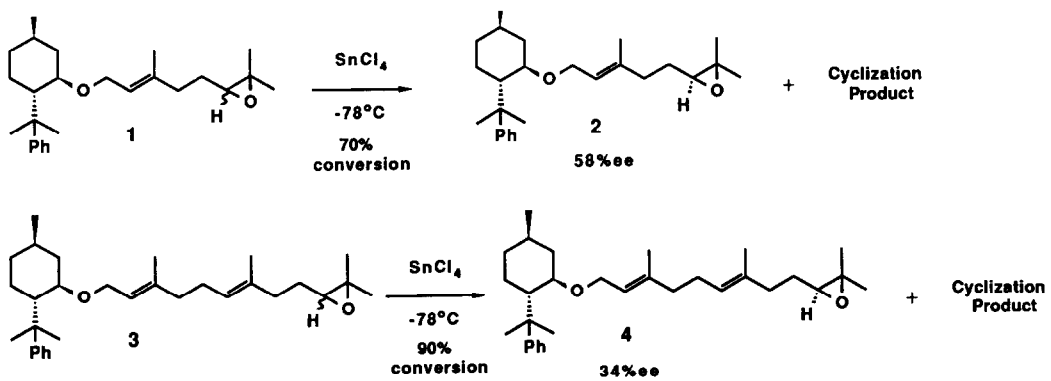
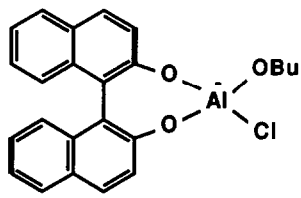
ABSTRACT: A short synthetic route to C_{16}-juvenile hormone is described which depends on new oxirane ring opening methodology and which also involves the joining of intermediate **8** and **12** in a one flask operation to construct the sesquiterpene structure.

This note describes a new synthetic route to C_{16}-Cecropia-juvenile hormone (**14**)[1] in optically active form. The synthesis is based on unique aspects of the chemistry of keto-epoxides and features the assembling of C_7- and C_8-segments of acyclic sesquiterpene in single process.

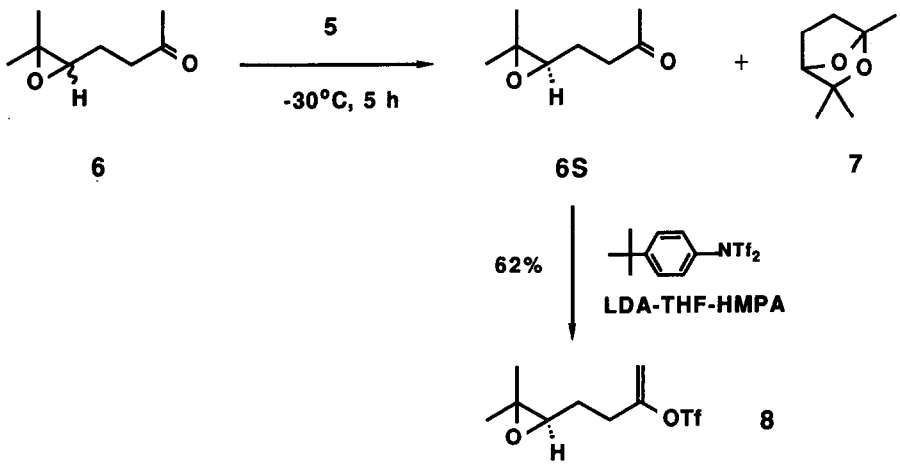
Past studies have revealed that the chiral anchimeric assistance in the epoxide ring opening process is possible and should provide a new route to optically active epoxide with the remote asymmetric induction, e.g. **1** → **2**[2] and **3** → **4**.[3] Thus, a high degree of chiral neighboring π-bond participation during S_N2-like epoxide ring opening should play an important role for the formation of A ring during the biological construction of steroid.[4] In parallel with these studies we have investigated an approach to the chiral Lewis acid catalyzed ring opening of epoxides in systems where a similar anchimeric assistance in the epoxide ring opening process can be expected.



Chiral Lewis acid **5**[5] was synthesized *in situ* from the R(+)-binaphthol, dimethylaluminum chloride, and lithium butoxide in dichloromethane. Use of this catalyst to cyclize the polyene terminal epoxides did not proceed smoothly at low temperature, and at the higher temperature the effective kinetic resolution could not be achieved. The aim of the present study was to see if we could enhance the rate of the ring opening by use of an appropriately placed cation stabilizer. Accordingly, we elect to compare the cyclization of **6** having the carbonyl auxiliary at C-6. Indeed, an efficient but unconventional process for the separation of the enantiomers **6** was thus developed: treatment of the racemate **6** with the freshly prepared **5** at -30°C for 5 h to give the optically pure epoxide R-**6**[6] in addition to the internal acetal **7**. This process is convenient and amenable to scale-up. The optically pure R-isomer can be obtained in ca. 20% yield from the readily available racemate **6**; higher yields are probably achievable. Recovery of binaphthol is excellent (>90%). The pure epoxide R-**6**, which was now shown to be a highly useful building block in acyclic terpene synthesis, was converted to the triflate **8** with triflic imide[7] and lithium diisopropylamide in THF- HMPA at low temperature.

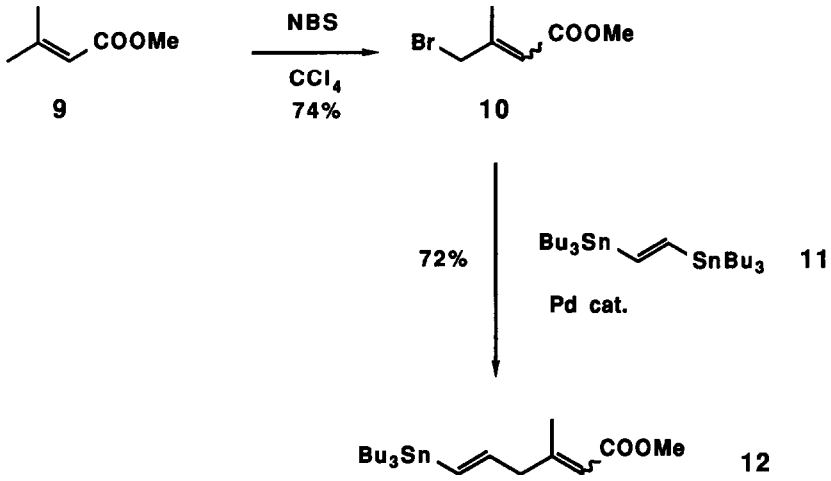


5

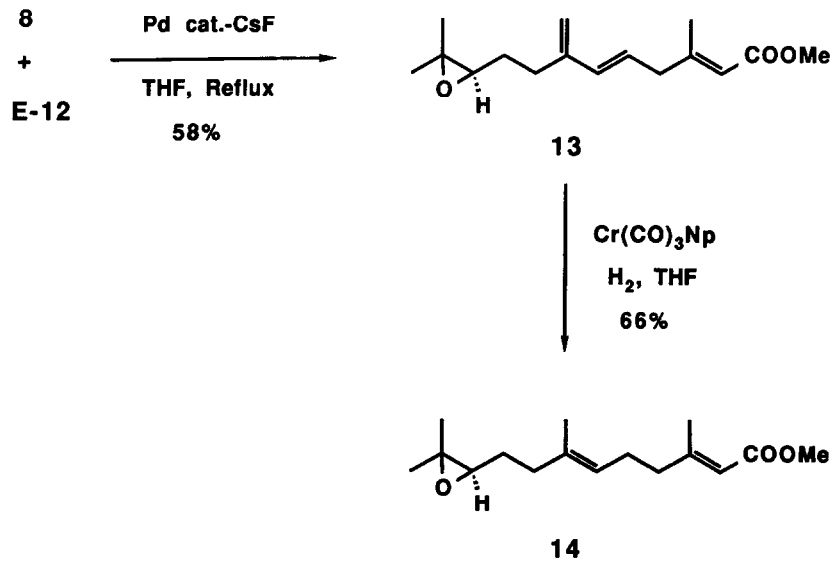


6 **6S** **7** **8**

The other component required for the assembly of juvenile hormone was obtained in a straightforward manner. Radical bromination of the ester **9** with N-bromosuccimide in carbon tetrachloride gave rise to the bromoester **10** (E/Z = ca. 1:1),[8] which was coupled with the ditin **11** in the presence bis(acetonitrile)dichloropalladium using the method of Stille[9] to afford the ester **12** in 72% yield. After careful chromatographic separation of the stereoisomer, the pure E-**12** was used for the subsequent coupling reaction.



The JH system was now assembled from components **8** and **12** as follows. A mixture of tetrakis(triphenylphosphine)palladium (2 mol%), cesium floride (3.0 equiv),[10] **8**, and **12** in dry degassed THF was heated at reflux for 5 h, after column chromatography on silica gel, to produce the desired triene **13** in 58% yield.[11] Partial and selective hydrogenation of **13** was accomplished in the presence of tricarbonyl[(1,2,3,4,4a,8a-η)naphthalene]chrominum catalyst[12] under 80 atm of H_2 in dry THF at 45°C for 5 h to afford the juvenile hormone **14** in 62% yield without contamination of any of the corresponding Z isomer.[13]



The above reported synthesis of juvenile hormone contains a number of noteworthy methodological elements including (1) the novel synthesis of optically active epoxide **6**, (2) the one flask process for the assembling of right and left hand side of sesquiterpene structure, (3) stereospecific construction of trisubstituted olefin using chrominum catalyzed hydrogenation of 1,3-diene.

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References and Notes

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6. $[\alpha]_D^{21}$ = 28.3° (c = 0.94, $CHCl_3$). The optical purity was determined with ^1H NMR analysis in the presence of $Eu(hfc)_3$, see ref. 2.
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11. IR (neat film) 3200-2800s, 1735s, 1660s, 1445m, 1230w; ^1H NMR ($CDCl_3$) δ 6.14 (d, 14 Hz, 1H), 5.70 (s, 1H), 5.66 (dd, 14 and 8.5 Hz, 1H), 5.00 (d, 2 Hz, 1H), 4.98 (d, 2 Hz, 1H), 3.70 (s, 3H), 2.93 (d, 8.5 Hz, 2H), 2.76 (t, 6 Hz, 1H), 2.42 (m, 1H), 2.31 (m, 1H), 2.16 (s, 3H), 1.73 (m, 2H), 1.31 (s, 3H), 1.26 (s, 3H); Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.7; H, 9.2. Found: C, 72.4; H, 9.1. $[\alpha]_D^{21}$ = 7.6° (c - 0.94, ether).
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13. IR (neat film) 3200-2800s, 1735s, 1660s, 1445m, 1235w, 1160s; ^1H NMR ($CDCl_3$) δ 5.68 (br. s, 1H), 5.15 (br. s, 1H), 3.69 (s, 3H), 2.71 (t, 6.8 Hz, 1H), 2.19 (s, 3H), 2.18 (s, 3H), 2.11 (m, 2H), 1.7-1.5 (m, 6H), 1.31 (s, 3H), 1.26 (s, 3H); Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.1, H, 9.8. Found: C, 71.9, H, 9.6; $[\alpha]_D^{21}$ = 5.4° (c = 0.6, methanol), lit. $[\alpha]_D$ = 5.75° (c = 0.4, methanol) for (R)-isomer, and $[\alpha]_D$ = -5.44° (c = 0.7, methanol) for (S)-isomer, see ref. 1.

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