Pergamon

Tetrahedron Letters, Vol. 38, No. 43, pp. 7491-7494, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01798-X

New Stereospecific Synthetic Routes to the Bicyclo[3.2.1]octane Subunit of the Kaurenoids and Gibberellins

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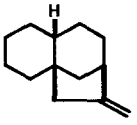
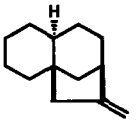
Summary: *Three new sequences are described for the synthesis of the bicyclo[3.2.1]octane core of diterpenoids such as the kaurenes (Schemes 1-3).* © 1997 Elsevier Science Ltd.

The tricyclic system **1** is a prominent feature of many naturally occurring diterpenoids, including kaurenoids and gibberellins (*ent*-kaurenoids). The biological importance and structural complexity of these natural products have stimulated an enormous body of research on their synthesis.[1] In connection with recent studies directed at the total synthesis of the potent anti-HIV kaurenoid neotripterifordin (**3**),[2] we have developed new stereocontrolled processes for the construction of **1** and also the *trans*-6/6-fused diastereomeric unit **2**, which are described herein.



1



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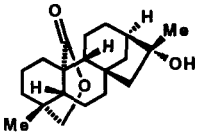


3

The first approach to the *cis*-6/6-fused subunit **1** is outlined in Scheme 1. Conjugate addition of the vinyl Gilman reagent to enone **4** produced stereospecifically the *cis*-fused β-vinyl ketone **5** in 95% yield.[3] Reduction of ketone **5** by $LiAlH_4$ followed by hydroxy protection produced TBS ether **6** in 94% yield. Hydroboration of the vinyl group in **6** and oxidation gave aldehyde **7** in 92% yield. One-carbon homologation of aldehyde **7** to alkyne **8** was achieved in high yield using the Seyferth-Gilbert reagent.[4] The corresponding xanthate prepared from alcohol **8** was treated with *n*-Bu_3SnH–AIBN in toluene at 110 °C to generate the cyclohexyl radical which underwent efficient cyclization to form **1** in 93% isolated yield.[5]

The success of the cyclization **8** → **1** prompted the study of a more direct route from **4** to **1** and led to the four-step synthesis which is shown in Scheme 2. Reaction of α,β-enone **4** and 1,2-propadienyltriphenylstannane[6] using $TiCl_4$ as catalyst in CH_2Cl_2 (-78 °C for 1 h and -40 °C for 16 h) afforded the *cis*-fused acetylenic conjugate adduct **9** stereospecifically in 82% yield at 50% conversion along with recovered **4**. Although this reaction could not be driven to completion, it provided a ready source of the acetylenic ketone **9** since **4** and **9** are easily separated by silica chromatography. This ketone was efficiently converted to **1** by the sequence: (1) reduction with $NaBH_4$–CH_3OH; (2) xanthate formation and (3) radical cyclization with *n*-Bu_3SnH–AIBN in toluene at 110 °C.

The conversion of α,β-enone **4** to the *cis*-fused propargylic conjugate adduct **9** represents the first instance of propargylic addition to this or any other structurally related cyclic α,β-enone. The reaction did not occur at all with 1,2-propadienyltri-*n*-butylstannane (some 1,2-carbonyl addition was observed with this reagent), 1,2-

propadienyltriphenylplumbane or 1,2-propadienyltrimethylsilane. It is clear that this potentially important reaction requires further study and development.[7]

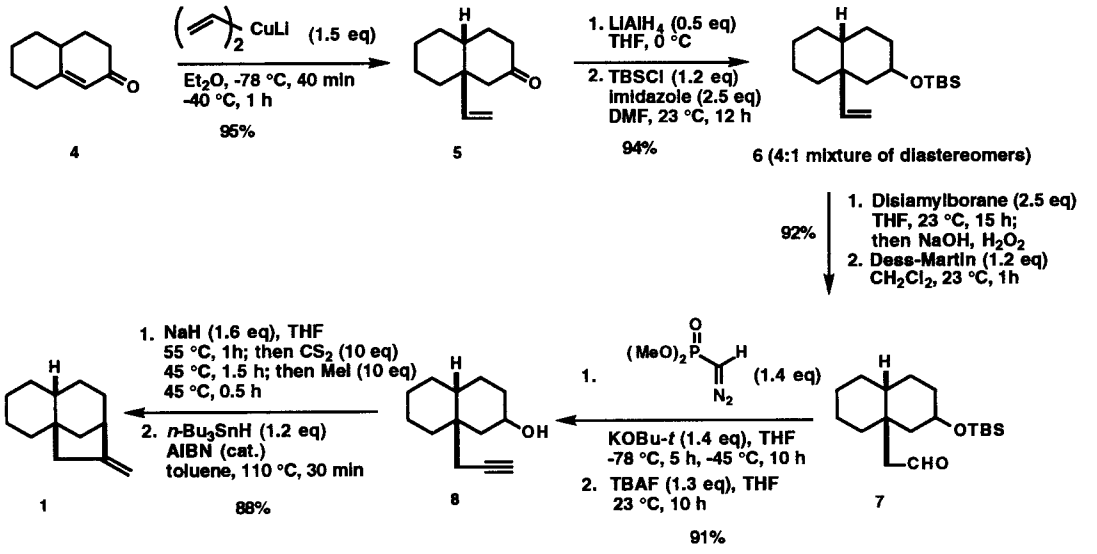
An efficient and stereocontrolled route to **2**, the tricyclic diterpene prototype containing a *trans* decalin subunit, was developed as outlined in Scheme **3**. The photoaddition of allene to **1** occurred rapidly and cleanly (450 watt, medium-pressure Hanovia Hg lamp for use with an immersion well) to give an almost quantitative yield of the adduct **10**.[8] Reduction of **10** with L-Selectride at -78 °C afforded stereospecifically the alcohol **11**.[9] The orientation of the hydroxyl group in **11** was inverted by Mitsunobu displacement using benzoic acid and hydrolysis, and the resulting diastereomer of **11** was converted to the corresponding mesylate **12** (92% overall from **11**). Reaction of mesylate **12** with $MeAlCl_2$ at -78 °C in CH_2Cl_2 proceeded by rearrangement of the β-olefinic carbon to give the rearranged chloride **13** in essentially quantitative yield.[10] Reductive dechlorination of **13** afforded **2**, the *trans*-6/6-fused diastereomer of **1** cleanly.

A different mode of rearrangement from **12** → **13** was observed with mesylate **14**, the diastereomer of mesylate **12**, as indicated in Scheme 4. Reaction of **14** with diethylaluminum bromide at -78 °C for 5 min provided in 91% yield the allylic bromide **15**, [11] the product of shifting the 6/4 fusion bond in a 1,2-carbon rearrangement. This interesting ring expansion reaction of an allene–α,β-enone photoadduct is a promising method for the synthesis of polycyclic terpenoids containing a fused pentalane subunit.

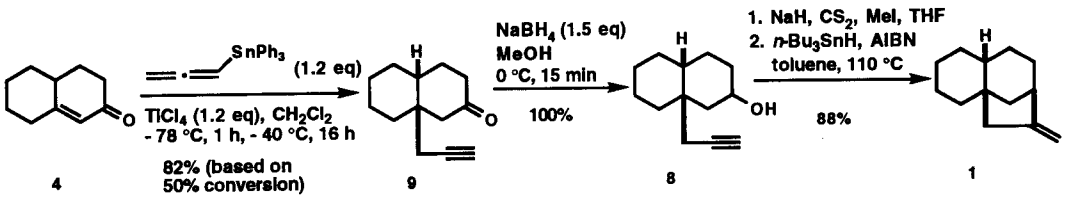
The observed rearrangements **12** → **13** and **14** → **15** can both be rationalized in terms of the assigned stereochemistry of **12** and **14** as concerted processes in which the migrating carbon moves backside to the carbon bearing the leaving group.

In summary the transformations outlined in Schemes 1-4 constitute useful new methodology for the synthesis of a variety of polycyclic structures, especially in the diterpenoid series.[12]

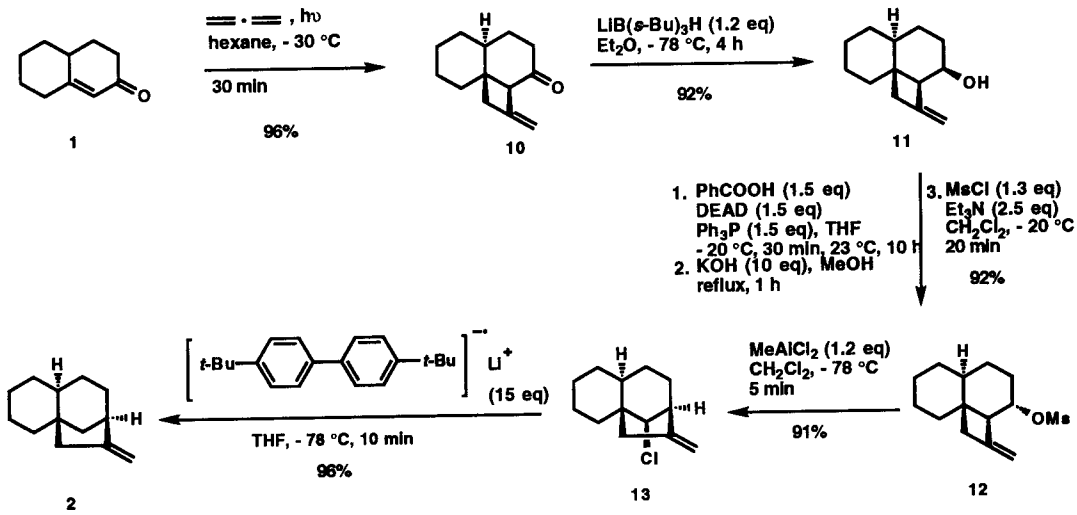
Scheme 1.



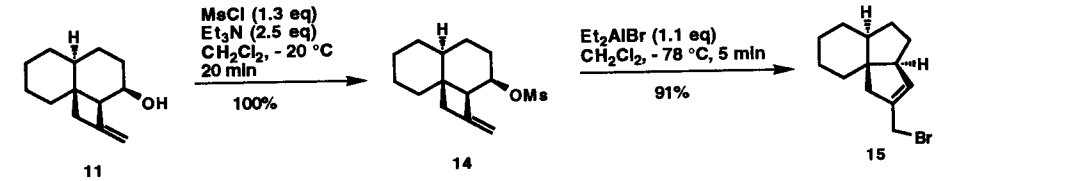
Scheme 2.



Scheme 3.



Scheme 4.



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5. For a review see Giese, B.; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969.
6. 1,2-Propadienyltriphenylstannane, m.p. 81-82.5 °C, is readily prepared by reaction of propargylmagnesium bromide in ether with triphenylchlorostannane at 23 °C followed by isolation and recrystallization from hexane. See Le Quan, M.; Cadiot, P. *Bull. Soc. Chim. Fr.* **1965**, 45.
7. The propargylation of unhindered, non-β-substituted α,β-enones presents no problems, see (a) Haruta, J.; Nishi, K., Matsuda, S.; Akai, S.; Tamura, Y.; Kita, Y. *J. Org. Chem.* **1990**, *55*, 4853. (b) Corey, E. J.; Rücker, C. *Tetrahedron Letters* **1982**, *23*, 719.
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9. The ^{1}H NMR data for alcohol **11** (carbinol C<u>H</u>–OH peak at 4.02 δ, dt, J = 12.0, 6.0 Hz) are consistent with a boat conformation of the six-membered ring in which the carbinol is a member. The boat arrangement is favored by the fusion with the four-membered ring. The stereochemistry assigned to **11** is also consistent with its formation by L-Selectride reduction of **10** and the ^{1}H NMR data for the epimeric alcohol: C<u>H</u>OH 3.92 δ (ddd, J = 8.0, 6.0, 5.2 Hz, 1 H).
10. The orientation of chlorine in **13** follows from the ^{1}H NMR spectrum; partial ^{1}H NMR data (500 MHz, $CDCl_3$): <u>H</u>CCl, 3.85 δ, s; C=C<u>H</u>$_2$, 4.95 and 4.93 δ; allylic C<u>H</u> 2.82 δ br s; allylic C<u>H</u>$_2$ 2.48 δ (d, J = 12 Hz, 1 H) and 2.18 δ (dt, J = 12.0, 1.9 Hz, 1 H). The <u>H</u>CCl and bridgehead <u>H</u>C dihedral angle for **13** is estimated to be 86°, whereas that for the diastereomeric chloride is expected to be 34° (from measurements with HGS models).
11. Partial ^{1}H NMR data for allylic bromide **15** (500 MHz in $CDCl_3$): one olefinic proton at 5.75 δ (s, 1 H); C<u>H</u>$_2$Br at 4.01 δ (s, 2 H); H<u>C</u>–C=C at 2.45 δ (m, 1 H); H_2CC=C at 2.21 δ (d, J = 12.0 Hz, 1 H) and 2.06 δ (d, J = 12.0 Hz, 1 H).
12. This research was supported by grants from the National Institutes of Health and the National Science Foundation.

(*Received in USA* 31 *July* 1997; *revised* 22 *August* 1997; *accepted* 25 *August* 1997)