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# A Direct Stereoselective Synthesis of (±)-14-Deoxyisoamijiol[§1]

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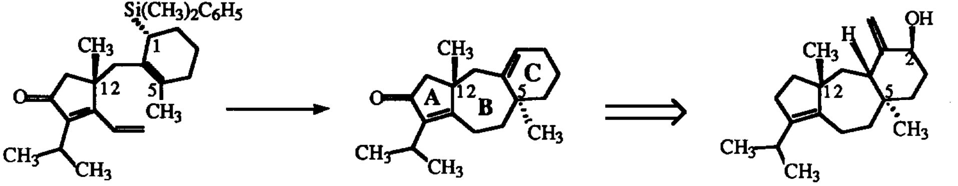
**Summary:** A 16-step total synthesis of (±)-14-deoxyisoamijiol is reported featuring an intramolecular Sakurai reaction to stereospecifically construct the dolastane skeleton.

The dolastanes are a group of marine diterpenes which possess a distinctive 5-7-6 linearly fused tricyclic framework. Although several research groups have successfully assembled the dolastane skeleton, their approaches are generally based on the so-called "A + B + C → ABC" strategy.[3,4] We have found intramolecular allylsilane additions an extremely powerful means for synthesizing a wide variety of carbocyclic systems.[5] Thus we felt that this methodology was versatile enough to construct the central seven-membered ring of the dolastanes via an "A + C → ABC" approach (cf. **2** → **3**, Eq. 1). Moreover, since many of our cyclizations proceed with remarkable diastereoselectivity[6] we were confident that cyclization would not only assemble the basic dolastane skeleton but, more importantly, also establish the correct stereochemical relationship between the C(5) and C(12) quaternary carbon atoms. This possibility served as the impetus for our synthesis of 14-deoxyisoamijiol.[7,8]

**Equation 1**



**2** **3** **14-Deoxyisoamijiol** (**1**)

Equation 2 details the synthesis of trienone **2**. Enone **5**[10] is converted into chloride **6**[9] using several well-established procedures. The coupling of **6** with the kinetic enolate of 3-ethoxy-2-isopropyl-5-methyl-2-cyclopenten-1-one (**4**)[11,12] affords a 3:2 mixture of diastereomers **7** and **8** in 88% yield. Addition of vinylmagnesium bromide, followed by mild acid hydrolysis, provides trienones **2** and **9** which are separable via silica gel chromatography.

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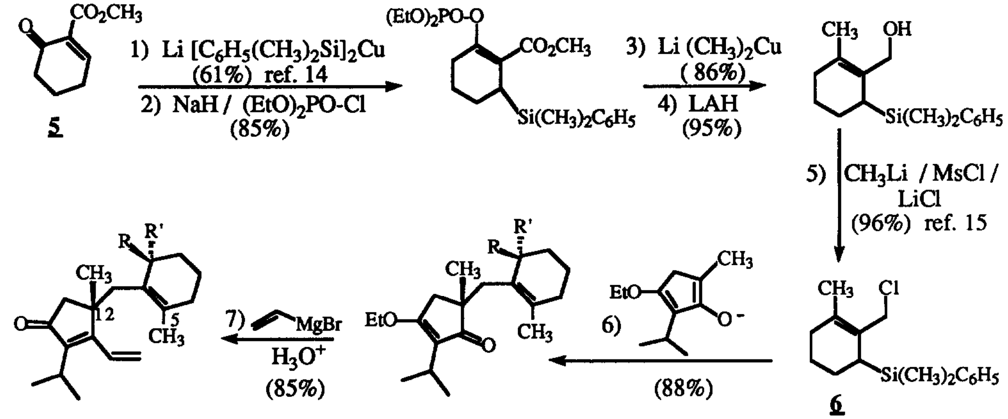
on the occasion of his receipt of the James Flack Norris Award

**Equation 2**

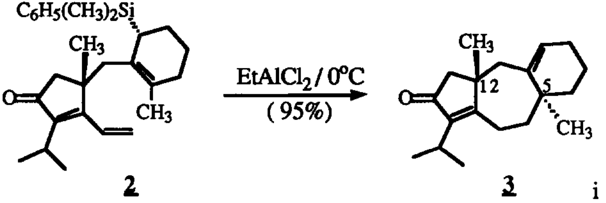


$R = H$; $R' = Si(CH_3)_2C_6H_5$ (2) $R = H$; $R' = Si(CH_3)_2C_6H_5$ (7)

$R = Si(CH_3)_2C_6H_5$; $R' = H$ (9) $R = Si(CH_3)_2C_6H_5$; $R' = H$ (8)

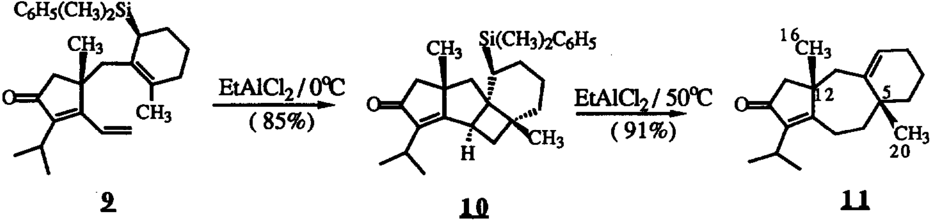
Treatment of **2** with ethylaluminum dichloride yielded enone **3** with a trans orientation of the C(5) and C(12) quaternary methyl groups in 93% overall yield (Eq. 3).[16] In contrast, reaction of **9** under

**Equation 3**



identical reaction conditions gave tetracyclic enone **10**, which results from the intramolecular alkylation of a cationic intermediate having a cis orientation of the C(16) and C(20) methyls (Eq. 4). Moreover, re-exposure of tetracyclic enone **10** with excess $EtAlCl_2$ (2.5 equivalents) at elevated temperatures gave tricyclic enone **11** with a cis relationship of the C(5) and C(12) methyls.

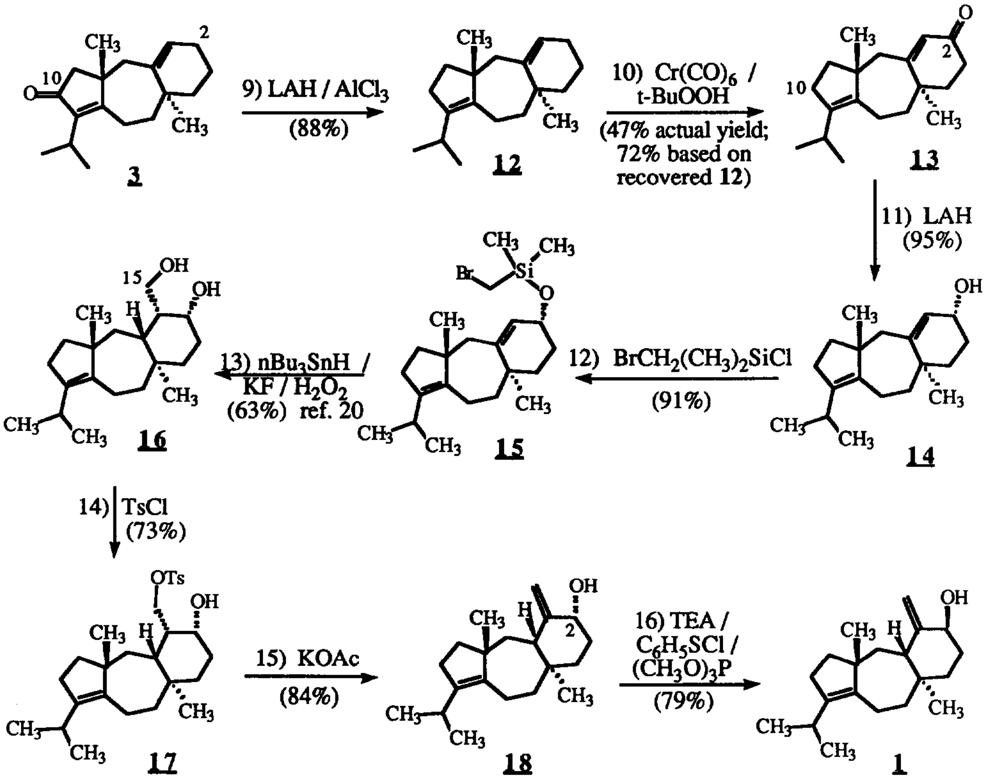
**Equation 4**



The oxidation states of the C(10) and C(2) carbons were interchanged by removal of the C(10) carbonyl with $LAH/AlCl_3$[18] to furnish diene **12**, followed by regiospecific oxidation at C(2) using

$Cr(CO)_6$ and tert-butyl hydroperoxide to give enone **13** in 47% yield, along with 29% unreacted **12** and 10% of a bis-enone in which oxidation had occurred at both C(2) and C(10).[19]

**Equation 5**



Establishment of the trans-BC ring fusion and introduction of the C(15) carbon atom was achieved using a procedure developed by Stork and Kahn.[20] In order to implement this methodology enone **13** was reduced with LAH to furnish allylic alcohol **14** with an α-oriented hydroxyl group. Silylation of **14** followed by radical-promoted cyclization and workup with KF and hydrogen peroxide gave diol **16** in 57% overall yield.

The final elaboration of the cyclohexane ring was achieved in three steps. Selective monotosylation of the primary hydroxyl group, followed by base-promoted 1,2-elimination, gave allylic alcohol **18** in 61% overall yield. The sulfenate derived from **18** smoothly rearranged to afford a sulfoxide which produced a new, thermodynamically favored sulfenate upon rearrangement;[21] desulfurization of this sulfenate results in the correct configuration at C(2)[22] and completes our synthesis. The NMR (300MHz), infrared, and mass spectra of synthetic racemic 14-deoxyisoamijiol were identical with those previously published.[7]

**Acknowledgement:** Support from the National Institute of General Medical Sciences through research grant 1 R01 GM39752 is gratefully acknowledged.

## References and Notes:

1. Taken in part from the Ph.D. dissertation of C. Ringold, *The University of Georgia,* 1989.
2. a) Author to whom correspondence regarding the synthesis of **1** should be addressed. b) Author to whom correspondence regarding the 2D NMR techniques employed to establish the structures of **2**,**3**, **9** and **10** should be addressed.
3. For recent dolastane syntheses, see: a) Pattenden, G.; Robertson, G. M. Tetrahedron Lett. **1986**, *27*, 399. b) Begely, M.; Pattenden, G.; Roberston, G. J. Chem. Soc. Perkin Trans. I **1988**, 1085. c) Mehta, G.; Krishnamurthy, N. Tetrahedron Lett. **1987**, *28*, 5945. For other dolastane-type diterpene syntheses, see: d) Piers, E.; Friesen, R. W.; J. Org. Chem. **1986**, *51*, 3405. e) Belmont, D. T.; Paquette, L.A. J. Org. Chem. **1985**, *50*, 4102. f) Paquette, L.A.; Lin, H.-S.; Belmont, D. T.; Springer, J. P. Ibid. **1986**, *51*, 4807. g) Piers, E.; Friesen, R. W. J. Org. Chem. **1986**, *51*, 3405.
4. For a failed "A + C → ABC" strategy featuring an intramolecular Michael addition, see ref. 3e.
5. For a review of intramolecular additions of allylsilanes to dienones, see: Majetich, G.; Hull, K.; Lowery, D.; Ringold, C.; Defauw, J. *Intramolecular Additions of Allysilanes to Dienones.* A chapter in "Selectivities in Lewis Acid-Promoted Reactions," **1989**, D. Schinzer, Ed., Kluwer Academic Publishers Group, Dordrecht, Holland.
6. A manuscript discussing the diastereoselectivity of dienone cyclizations is in preparation.
7. *For the isolation of 14-deoxyisoamijiol,* see: Ochi, M.; Asao, K.; Kotsiki, H.; Miara, I.; Shibata, K. Bull. Chem. Soc. Jpn. **1986**, *59*, 661.
8. a) All structures drawn here represent racemates, only one enantiomer being drawn. b) Reaction conditions have not been optimized. c) All yields are isolated yields. b) The spectroscopic data obtained for all new compounds were consistent with the assigned structures.
9. Chloride **6** has been independently prepared via the identical sequence of reactions, see: Akers, J.A.; Bryson, T. A. Tetrahedron Lett. **1989**, *30*, 2187.
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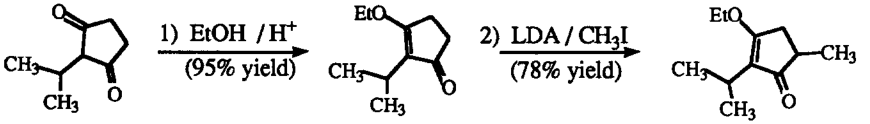
12. Enone **4** was prepared from 2-isopropyl-1,3-cyclopentanedione[13] as follows:



**4**

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16. In acyclic systems, allylsilanes generally react with electrophiles with high *anti* selectivity due to the steric bulk of the silyl moiety, while the work of Fleming et. al.[17] with cyclic allylsilanes demonstrated that electrophiles can also add *syn* to the silyl moiety. Note that the allylsilane of **2** reacts with *anti* selectivity, despite its cyclic nature.
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