Total Synthesis of Endiandric Acid A via an Intramolecular Diels-Alder Strategy

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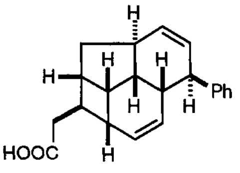
Received 27 September 1996

Dedicated to Professor E.J. Corey in recognition of his numerous contributions to organic chemistry

Abstract. The total synthesis of endiandric acid A (**1**), featuring an intramolecular Diels-Alder approach for elaboration of the 6-5-6 carbocyclic array and an intramolecular Majetich reaction for construction of the four-membered ring, is described.

Endiandric acid A (**1**) is a tetracyclic carboxylic acid isolated from the leaves of *Endiandra introrsa* (Lauranceae), a plant indigenous to Australia. The structure of **1** was unambiguously established by Black and co-workers in 1980 using single crystal x-ray analysis.[1] The occurrence in nature of **1** in racemic form led Black to postulate a non-enzymatic pathway to **1** *via* a series of cascading cyclizations.[2] In 1982 Nicolaou and co-workers[3] reported a total synthesis of **1** which featured a series of cascading electrocyclizations modeled after Black's hypothesis. We detail below a total synthesis of endiandric acid A which employs an intramolecular Diels-Alder strategy for elaboration of the 6-5-6 carbocyclic skeleton.



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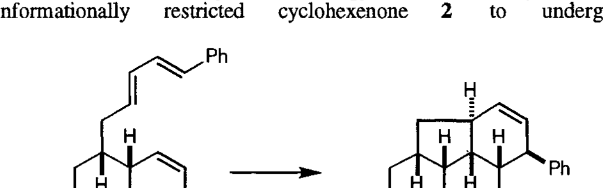
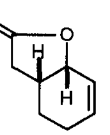
Central to our synthetic strategy was the ability of the conformationally restricted cyclohexenone **2** to undergo intramolecular [4+2] cycloaddition *via* an exo transition state[4] leading to the formation of tricyclic ketone **3**. Subsequent elaboration of the four-membered ring would provide access to endiandric acid A.



2 **3**

Synthesis of cyclohexenone **2** commences with the known bicyclic lactone **4**.[5] Alkylation (LDA, THF, HMPA, -78°C→RT) of **4** with bromide **5**[6] gave rise exclusively to **6** in 91% yield.



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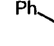

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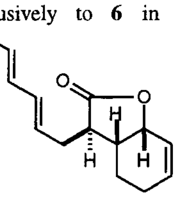

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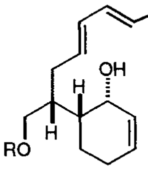
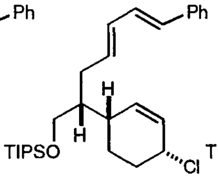
Reduction (LiAlH$_4$, Et$_2$O, 0°C, 2.5 h) of lactone **6** afforded crystalline diol **7**, mp 79-80°C, which upon exposure (5 h) to triisopropylchlorosilane in methylene chloride containing 4-dimethylaminopyridine and imidazole afforded **8** in 99% overall yield.



7 (R = H)
8 (R = TIPS)



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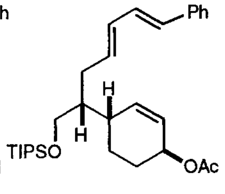

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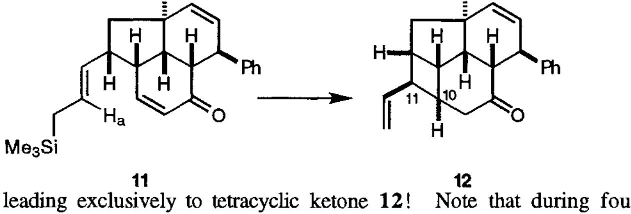
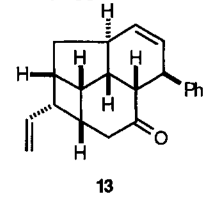
Conversion of **8** to the allylically transposed cyclohexenone **2** met with some difficulty. All efforts to rearrange the corresponding allylic acetate of **8** using palladium catalysis[7] met with failure. However, treatment of **8** with thionyl chloride in methylene chloride containing 10 mol% dimethylaminopyridine gave the allylic transposed chloride **9** which upon exposure to tetramethylammonium acetate[8] in refluxing acetone afforded **10** in 73% overall yield. Treatment of **10** with potassium carbonate in methanol followed by allylic oxidation (MnO$_2$, CH$_2$Cl$_2$, 12 h) provided cyclohexenone **2** in 91% yield.

With cyclohexenone **2** in hand we set out to examine the conversion of **2** into **3**. Much to our surprise, exposure of **2** to 5.0 M lithium perchlorate in diethyl ether gave rise to no cycloadduct. The starting material was completely recovered. In contrast, addition of 10 mol% trifluoroacetic acid to a 0.01 M solution of **2** in 5.0 M lithium perchlorate-diethyl ether[4] provided after 5 min at ambient temperature a 90% yield of tricyclic ketone **3**.[9] Equally effective in promoting the intramolecular [4+2] cycloaddition was trimethylsilyl triflate. Brief treatment (1 min) of a 0.01 M solution of **2** in methylene chloride with 10 mol% trimethylsilyl triflate afforded a 90% yield of **3**.[9] Under conventional thermal conditions (toluene, 110°C) the reaction required 36 h in order to go to completion and gave rise (91%) to a mixture of cycloadduct **3**, along with the corresponding endo isomer, in a ratio of 7.7:1.

Completion of the synthesis of endiandric acid A necessitated elaboration of a four-membered ring onto the 6-5-6 carbocyclic system of **3**. It was anticipated that the allylsilane **11** derived from **3** would undergo an intramolecular Majetich cyclobutane annulation reaction[10] leading exclusively to tetracyclic ketone **12**! Note that during four membered ring formation the often observed 1,2-addition products are not possible in the case of **11**→**12**. Furthermore the stereochemistry at C(10) and C(11) is assured. With respect to the stereochemistry at C(10), the allylsilane can only approach the enone from the α-face. In the case of the configuration at C(11), Dreiding models clearly reveal a serious interaction between H$_a$ and H$_b$ (*cf* structure **11**) in the transition state leading to the C(11) epi compound **13**.



11 **12**



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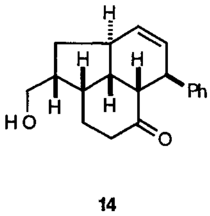
In order to examine if our hypothesis regarding four-membered ring formation with complete control of stereochemistry was a viable strategy, tricyclic ketone **3** was transformed into allylsilane **11**. Treatment (12 h) of **3** with tetra-n-butylammonium fluoride in tetrahydrofuran gave rise to a quantitative yield of **14**, mp 121-123°C, which was converted into allylsilane **15** in 68% overall yield by a two-



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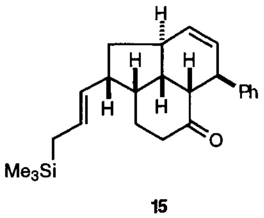

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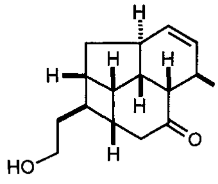
step sequence: Swern oxidation followed by immediate treatment of the resultant aldehyde with Seyferth's reagent.[11] Introduction of the enone moiety was realized in straightforward fashion (71% overall yield) *via* organoselenium chemistry.

With substrate **11** available, attention was focused on four-membered ring formation. Treatment of a 0.3 M solution of **11** in dimethylformamide containing 5.0 equiv of hexamethylphosphoramide with 0.2 equiv of tetra-n-butylammonium fluoride in the presence of powdered 4Å mol sieves gave rise in 65% yield to a single tetracyclic ketone, as evidenced by the ^{1}H NMR spectrum. Unequivocal proof of structure follows from conversion of **12** into endiandric acid A.

Completion of the synthesis of **1** required hydroboration of the vinyl group. Much to our surprise, hydroboration proved to be problematic. Use of conventional reagents (9-BBN, thexylborane, diisoamyborane) led to recovery of starting material which suggested that the configuration at C(11) was incorrect. Fortunately this proved not to be the case and the hydroboration problem was overcome by employing Evans' rhodium catalyzed hydroboration protocol.[12] Thus treatment of **12** with 2.0 equiv of catecholborane in tetrahydrofuran containing a catalytic amount of freshly prepared tris(triphenylphosphine)-rhodium(I) chloride[13] followed by standard basic hydrogen peroxide workup resulted in the formation of alcohol **16** in 84% yield. Prior to oxidation of the primary hydroxyl, the $\Delta^{8,9}$ olefin of endiandric acid A was introduced *via* a Shapiro olefination sequence.[14] Hydrazone formation (3.0 equiv trisylNHNH$_2$, 0.3 equiv *p*-TsOH, 10 equiv MgSO$_4$, 24 h) proceeded smoothly giving rise to the corresponding hydrazone in 95% yield. Exposure of the hydrazone to excess n-butyllithium gave rise to a complex mixture due to deprotonation at the benzylic carbon. Use of excess lithium diisopropylamide in tetrahydrofuran containing diisopropylamine gave rise after 4 h to a 50% yield of **17** along with 30% of recovered starting hydrazone. Oxidation (Dess-Martin periodinane[15] followed by silver oxide) of **17** produced (60%) crystalline endiandric acid A, mp 145-149°C (lit mp 147-145°C) whose structure was confirmed by single-crystal x-ray analysis.



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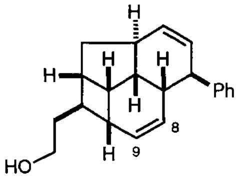

17

Acknowledgement. This investigation was supported by a Public Health Service Research Grant from the National Institutes of General Medical Sciences (GM 33605).

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