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Total Synthesis of α–Cedrene : A New Strategy Utilizing *N*-Aziridinylimine Radical Chemistry

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Abstract: Tandem free radical cycloaddition reaction of the N-Aziridinylimine intermediate produced tricyclo[5.3.1.$0^{1,5}$]undecane skeleton stereoselectively. A total synthesis of α–cedrene was completed in three step sequence from the cyclization product.

Keywords: Cycloadditions; Radicals and radical reactions; Imines; Natural products

Tandem radical cyclizations[1] have become one of powerful synthetic methodologies since the introduction of the tinhydride method in free radical chemistry.[2] *N*-Aziridinylimines have emerged as good substrates for the tandem radical cyclization reactions with their unique ability to serve as radical acceptors and donors at the same time.[3] This tandem reaction offers a method to construct quaternary carbon centers directly from carbonyl carbons. Since the construction of quaternary carbon centers from carbonyl carbons is not considered a favorable process and is generally avoided during synthetic planning, *N*-aziridinylimine radical chemistry would provide new strategies in organic synthesis. There have been few methods developed for the construction of quaternary carbon centers with limited applicability.[4] The tandem radical cyclization reaction of *N*-aziridinylimines offers a versatile and general method of constructing quaternary carbon centers. Application of *N*-aziridinylimine radical chemistry to the natural product synthesis has been successfully demonstrated by the total synthesis of modhephene and zizaene.[5] Herein we report a yet distinct application of tandem radical cyclization reaction of *N*-aziridinylimines for the construction of complex polycyclic structures.

Cedrene, a tricyclic sesquiterpene compound, has the tricyclo[5.3.1.$0^{1,5}$]undecane skeleton with two quaternary carbon centers. There are several natural products with this tricyclic skeleton[6] and several total syntheses of these compounds have been reported.[7] In most of the synthesis, the tricyclic ring system was constructed in the same order of bond formation. The spirocycle of the A and C rings was synthesized first and then the B-ring was constructed onto the spirocyclic ring either in separate operations or through a tandem reaction sequence. Though the stereochemistry at the C-2 carbon center can be used to control the relative

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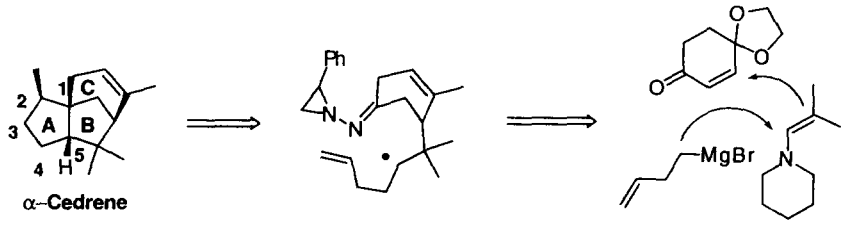
stereochemistry during the construction of the tricyclic system, none of the previous syntheses demonstrated good stereoselectivity except for the synthesis through the arene-olefin photo cycloaddition reaction strategy.[8]

Our synthetic strategy focused on the construction of the C-1 quaternary center from the corresponding cyclohexane ring system using the tandem radical cyclization reaction of a *N*-aziridinylimine (Scheme 1).

Scheme 1



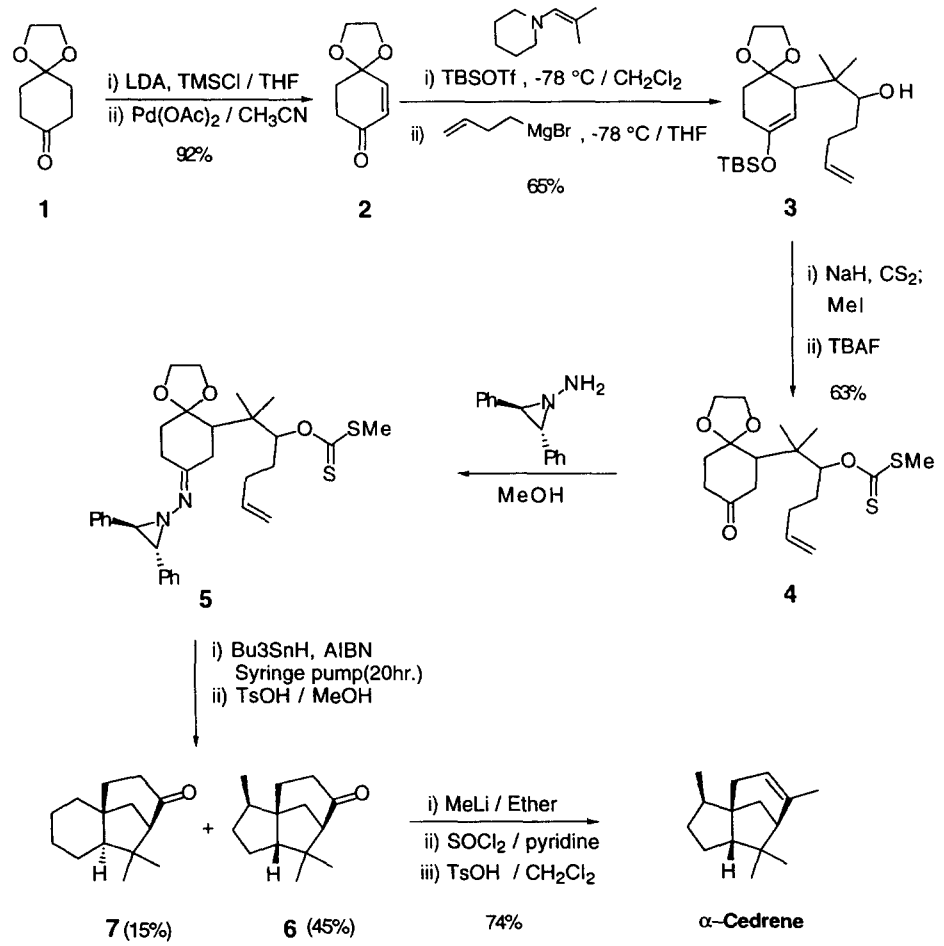
α-Cedrene

The precursor for the radical cyclization could be prepared from cyclohexenone, isobutyryl aldehyde anion and 3-butenyl anion through sequential reactions. Since the bond formation between the C-1 and the C-2 carbon centers becomes the last step of the tandem cyclization reaction, the bicyclic B,C ring system would control the stereochemistry of the C-1 methyl group during the final cyclization reaction. Examination of the conformations of the radical intermediate suggests that the desired isomer would be the major product through the favored chair-like transition state.[9] The tandem radical cyclization reaction also relies on the stereoselective formation of the [3.2.1]bicyclic system of the first radical cyclization reaction. The stereoselectivity of the first cyclization reaction was thought to be favorable for the formation of the desired stereoisomer since the butenyl appendage would adopt sterically less encumbered *exo*-position over the *endo*-position. With the anticipation that the tandem radical cyclization reaction would proceed stereoselectively, the total synthesis of cedrene started with the preparation of cyclohexenone **2** which has a protected ketone for the introduction of the methyl group onto the C-ring at a later stage of the synthesis.

Enone **2** was prepared from commercially available cyclohexanedione *mono*-ethylene ketal **1** through TMS enol ether formation followed by palladium mediated oxidation.[10] Compound **2** was treated with TBSOTf and the piperidine enamine of isobutyryl aldehyde to produce the conjugate addition product that provided an aldehyde with a protected ketone.[11] To this aldehyde, butenyl magnesium bromide was added to afford the alcohol **3** as a single diastereoisomer (determined from ^{1}H- and ^{13}C-N.M.R. spectra). The next stage of the synthesis is the introduction of a radical precursor at C-5 and conversion of the C-1 ketone into the *N*-aziridinylimine. The C-5 alcohol was transformed into the xanthate[12] and the enol ether was liberated to produce **4**. The ketone **4** was transformed into the *N*-aziridinylimine and the crucial tandem radical cyclization reaction was performed under high dilution conditions. When the radical cyclization reaction was performed with the usual *N*-

phenylaziridinylimine, the reaction was very sensitive to the reaction condition and the reaction was often complicated by the formation of styrene adduct.[13] To minimize formation of the undesired reaction product, aziridinylimine **5** was prepared from *N*-diphenylaziridinylamine[14] since stilbene was believed to be less reactive than styrene toward radical intermediates.

Scheme 2



The radical cyclization reaction of **5** proceeded smoothly without any complication. After deprotection of the ketal, 15-norcedran-8-one **6** was obtained as the major product along with tricyclo[6.3.1.$0^{1,6}$]dodecane **7**. The structure of **6** was confirmed through comparison of their spectroscopic data with those previously reported.[15] The stereoselectivity of the tandem radical cyclization reaction at C-1(β:α = 6.5:1) was compatible to the stereoselectivity observed during the formation of the tricyclo[6.2.1.$0^{1,5}$]undecane ring system.[5b] The structural identity of **7**[16] was deduced from the reported synthesis of **7**.[17]

15-Norcedran-8-one **6** was further transformed into α-cedrene using modified procedure of the published sequence.[15a] Methylation and dehydration of the ketone followed by isomerization using *p*-TsOH in CH_2Cl_2[18] completed the total synthesis. The spectral data of synthetic α-cedrene was identical to the spectroscopic data of natural α-cedrene.

In summary, the tandem radical cyclization reaction of *N*-aziridinylimines has provided a new efficient and stereoselective synthetic strategy to tricyclo[5.3.1.$0^{1,5}$] undecane ring system as demonstrated by the total synthesis of cedrene.

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[16] **7**: ^{1}H NMR ($CDCl_3$, 200MHz) δ 0.73 (s, 3H), 1.05 (s, 3H), 1.23-1.54 (m, 8H), 1.67-1.72 (m, 1H), 1.76-1.82 (bd, J=12.1Hz, 2H), 1.89-2.13 (m, 2H), 2.15- 2.23 (m, 1H), 2.28-2.35 (m, 2H). ^{13}C NMR ($CDCl_3$, 50MHz) δ 21.29 (CH_2), 21. 46 (CH_2), 21.67 (CH_3), 23.42 (CH_2), 26.64 (CH_2), 33.35 (CH_3), 34.39 (CH_2), 38.37 (CH_2), 40.26 (C), 40.62 (CH_2), 42.28 (C), 57.98 (CH), 62.00 (CH), 207.87 (CO). IR (thin film) 2930, 1711 cm^{-1}. MS (m/z): 206, 188, 163, 147, 121, 93.

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