Efficient Synthesis of *dl*-Zizaene Sesquiterpenes via Tandem Radical Cyclizations of *N*-Aziridinylimines

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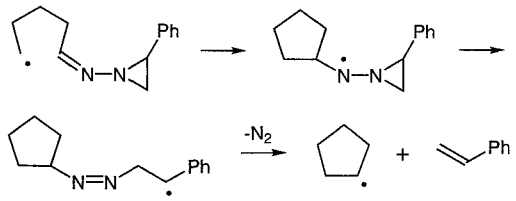
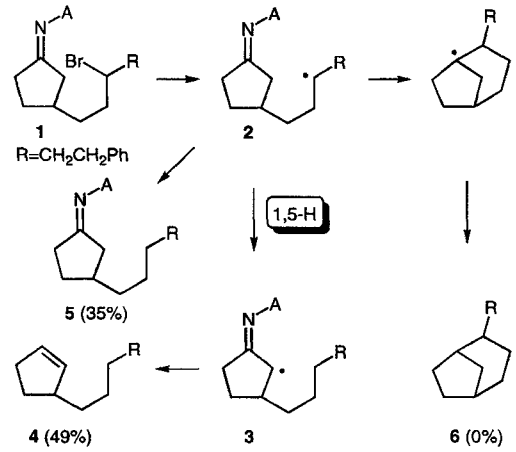
Abstract: Tandem radical cyclizations of *N*-aziridinylimine **7**, **17**, and **21** with Bu_3SnH/AIBN provided bicyclo[3.2.1]octanes and tricyclo-[6.2.1.$0^{1,5}$]undecanes, respectively and led to the stereocontrolled synthesis of *dl*-zizaene and *dl*-khusimone.

Radical reactions have attracted a great deal of recent attention[1] and they proved to be increasingly important in the synthesis of natural products, especially sesquiterpenes.[2] Previously we reported radical reactions of *N*-aziridinylimines (Scheme 1).[3] Among several unique features found in this reaction, of synthetic importance is (i) the generation of 5- and 6-membered ring radicals from acyclic precursors and (ii) the consecutive carbon-carbon bond formations at the same carbon. Thus, *N*-aziridinylimines can be used as a geminal radical acceptor and donor.[4] Based on these characteristics involving radical reactions of *N*-aziridinylimines, we recently reported an efficient method for the synthesis of *dl*-modhephene.[5]

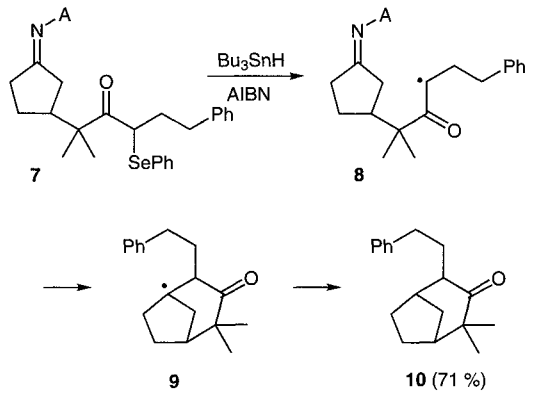


Scheme 1

As extension of this approach, we initially studied the possibility of constructing bicyclo[3.2.1]octanes (Scheme 2). When **1** was treated with Bu_3SnH/AIBN in refluxing benzene under a high dilution, **4** was isolated in 49% yield along with the direct reduction product **5** (35%) without yielding bicyclo[3.2.1]octane **6**. Apparently, 1,5-hydrogen transfer from **2** must occur, yielding **3** which underwent consecutive β-eliminations to afford **4**. However, the problem of obviating 1,5-hydrogen transfer was successfully solved by the use of more stable radicals (Scheme 3). When **7** was subjected to the similar conditions, the desired product **10** was obtained in 71% yield, indicating that 1,5-hydrogen transfer was completely suppressed by using stable radical **8**.[6]

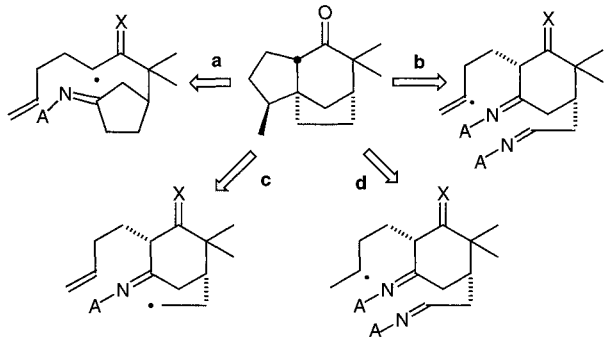


Scheme 2



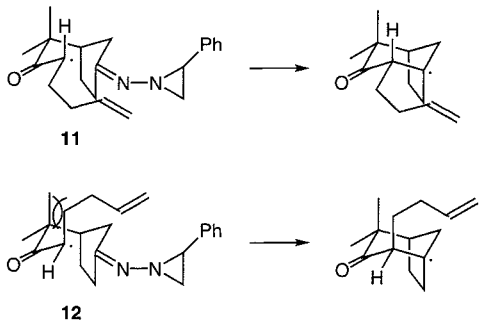
Scheme 3

Encouraged by this result, we turned our attention to the synthesis of zizaene sesquiterpenes such as *dl*-zizaene, *dl*-isokhusimone, and *dl*-khusimone. Zizaene sesquiterpenes have been the subject of considerable synthetic interest in 1970's and several key approaches to construct the tricyclo[6.2.1.$0^{1,5}$]undecane skeleton involved an intramolecular diazoalkane-carbonyl ring expansion,[7] an intramolecular magnesium-ene reaction,[8] and a titanium-promoted reductive coupling.[9,10] To construct the zizaene skeleton utilizing a consecutive carbon-carbon bond formation approach based on radical cyclization of *N*-aziridinylimines,[11] several synthetic approaches can be envisaged as shown in Scheme 4 and approach **a** seemed to be the most promising among four approaches because (i) it is expected that radical cyclization would provide the correct stereochemistry at the ring junction required in the synthesis of zizaene and (ii) it would be difficult to control the *cis*-stereochemistry of two substitutents in other approaches (**b**, **c**, **d**). As shown in Scheme 5, intermediate **12** would be disfavored due to strong steric interaction, as compared with **11**. Moreover, *gem*-dimethyl group would be beneficial for selective *N*-aziridinylimine formation.



Scheme 4

Our synthetic route to the target molecule is outlined in Scheme 6. The starting material **13** was readily prepared in 78% yield by TBSOTf promoted conjugate addition of piperidine enamine of isobutyl aldehyde to 2-cyclopenten-1-one in methylene chloride at -78 °C.[12] Treatment of **13** with α-phenylselenoalkyl lithium, generated in situ from phenylselenoacetal **14** and n-butyllithium, followed by Swern oxidation



Scheme 5

provided the key intermediate **16** after treatment with aqueous HCl. **16** was treated with *N*-aminoaziridine to yield imine **17** in 93% yield. Radical cyclization of **17** with Bu_3SnH/AIBN in refluxing benzene under highly diluted conditions afforded a 1:5 mixture of α- and β-isomer of **18** in 67% yield.[13] As predicted, the correct *trans*-fused product **18** was obtained and its structure was determined on the basis of ^1H NMR, ^{13}C NMR, IR, HRMS, and the reported spectral data.[14,15] Since it was reported that **18** was converted into *dl*-zizaene,[7a] a formal total synthesis of *dl*-zizaene is accomplished.

Khusimone belongs to zizaene family and its structure is closely related to the structure of zizaene. Thus, a similar synthetic scheme was adopted as shown in Scheme 7. Treatment of **13** with α-selenoalkyl lithium salt of **19** followed by Swern oxidation, subsequent hydrolysis and selective *N*-aziridinylimine formation provided **21** in high yield. **21** was subjected to the highly diluted radical cyclization conditions to afford a 2:1 mixture of **22** (78%) having the correct stereochemistry at the stereogenic centers. After the addition of methyllithium to the ketone group, vinylsilane was converted into **25** by removal of trimethylsilyl group with 10% aqueous HCl and subsequent oxidative cleavage with RuO_2/$NaIO_4$. Treatment of **25** with thionyl chloride and pyridine afforded *dl*-isokhusimone (**26**), which was reported to be converted into *dl*-khusimone.[16]

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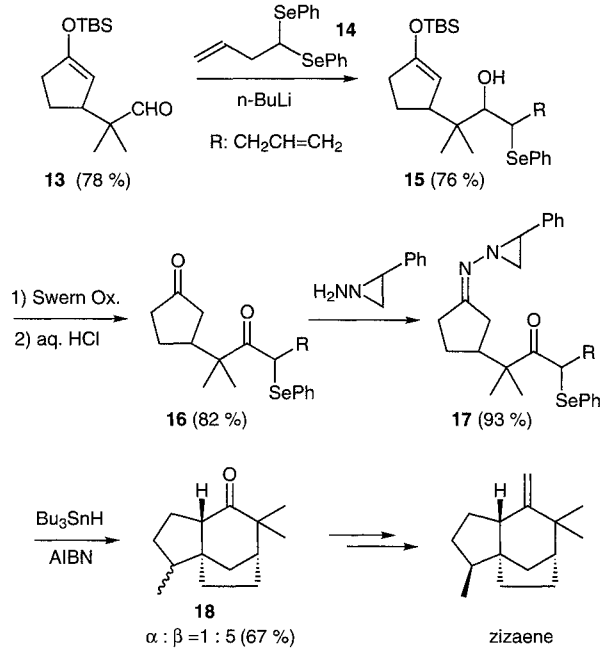

Scheme 6

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(1) For recent reviews, see : (a) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (b) Curran, D. P. *Synthesis* **1988**, 417, 489. (c) Curran, D. P. In *Comprehensive Organic Synthesis* ; Trost, B. M.; Flemming, I., Eds ; Pergamon : Oxford, **1991**; *Vol. 4*, p 715-831. (d) Fevig, T. L.; Curran, D. P.; Jasperse, C. P. *Chem Rev.* **1991**, *91*, 1237.

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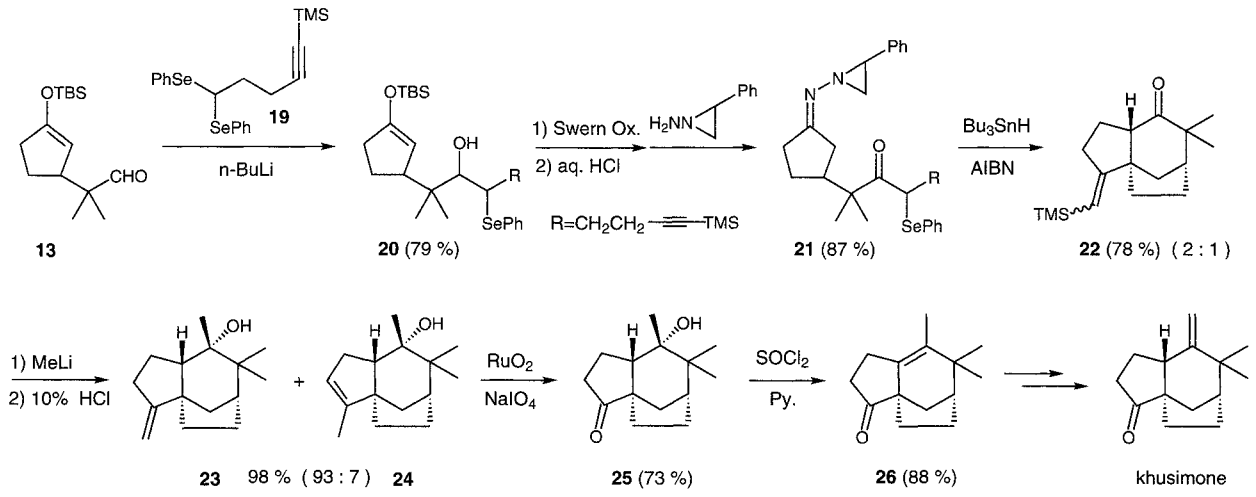

Scheme 7

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(13) A solution of **17** (136mg, 0.28 mmol) in benzene (55 ml, 0.005M) and a solution of Bu_3SnH (177 mg, 0.61 mmol) and AIBN (14 mg, 0.3 equiv) in benzene (20 ml, 0.03M) were degassed for 30 min with nitrogen, respectively. The solution of Bu_3SnH and AIBN was dropwise added to the refluxing benzene solution of **17** for 30 h by a syringe pump. After being stirred for additional 2 h, the reaction mixture was concentrated and purified by silica gel column chromatography to give **18** (38 mg, 67%).

(14) ^{1}H-NMR (300MHz, $CDCl_3$) : δ 2.90 (t, J=7.5Hz, 0.8H), 2.75 (t, J=7.5Hz, 0.2H), 2.10 (m, 1H), 2.01 (m, 1H), 1.85-1.77 (m, 3H), 1.65-1.50 (m, 5H), 1.44 (m, 1H), 1.24 (m, 1H), 1.17 (s, 3H), 1.02 (s, 3H), 0.95 (d, J=6.9Hz, 2.5H), 0.87 (d, J=6.6Hz, 0.5H). ^{13}C-NMR (75MHz, $CDCl_3$, β-isomer) : δ 216.5, 57.5, 54.0, 50.0, 49.0, 41.4, 36.2, 32.2, 30.5, 26.8, 25.7, 22.2, 20.1, 19.2. HRMS calcd for $C_{14}H_{22}O$: 206.1671, found 206.1672.

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