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A tandem radical cyclization route to tricyclo[4.3.*n*.0^{1,5}]alkanes

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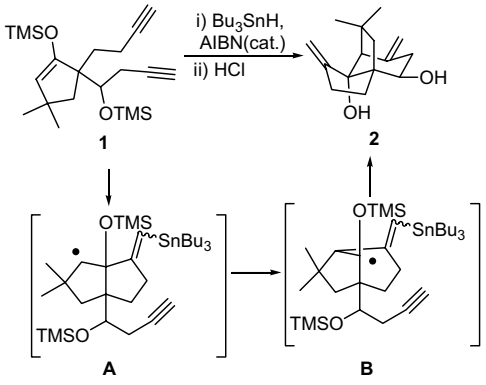
Abstract—A facile route to tricyclo[4.3.*n*.0^{1,5}]alkane skeletons from conjugated cyclic enones was developed through tandem free radical cyclization reaction sequence involving the cyclopropylmethyl radical mediated rearrangement. The scope and limitation of the reaction was investigated.

Since the introduction of trialkyltin hydride mediated radical cyclization reaction,[1] free radical cyclization reaction has been one of the most widely used synthetic methodologies in organic synthesis.[2] Vinyl radical cyclization reaction has been particularly interesting to us since the cyclization reaction could produce the 6-*endo* product as well as the 5-*exo* product through cyclopropyl methyl radical mediated rearrangement.[3] Based on the observations of the rearrangement in organic synthesis,[4] we envisioned a tandem radical cyclization reaction to construct tricyclo[4.3.2.0^{1,5}]undecane structure from cyclopentane ring and successfully executed the idea in the total synthesis of suberosenone (Scheme 1).[5] It was



Scheme 1. Tandem cyclization through rearrangement.

believed that the trialkyltin hydride mediated radical cyclization reaction of **1** produced tricyclic compound **2** via intermediate **A** and the rearranged intermediate **B** as the direct radical cyclization of **A** would be less favorable due to the strain energy associated in the transition state to form the bicyclic structure. With the successful construction of the tricyclic structure and the completion of the total synthesis of suberosenone, we became interested in generalization of the cyclization reaction.

Herein, we report the scope and limitation of this cyclization reaction.

First, several substrates with various substitution patterns were prepared from cyclopentenone or 2-methyl cyclopentenone by addition of butynyl Grignard reagent or butenyl Grignard reagent followed by allylation or propargylation to furnish the enyne compounds. The two-step process offered a quick entry into various substrates. The substrates were subjected to the standard radical cyclization reaction conditions for enynes[6] and the products were treated with SiO_2 or 1% HCl(aq)/MeOH for the destannylation reaction. The result was summarized in Table 1.

The cyclization reaction appeared to be quite general as all the substrates underwent tandem cyclization reaction when W was the methyl group that was believed to drive the rearrangement toward the more stable tertiary radical intermediates like **B** in Scheme 1 (entries 1–5). When W was the hydrogen that could not provide extra stabilization after the rearrangement, neither rearrangement nor tandem cyclization reaction was observed (entry 6).

Keywords: Radical; Cyclization; Mechanism.
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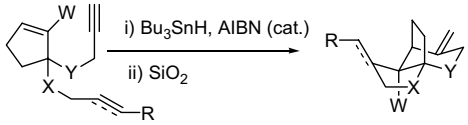
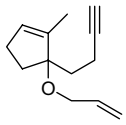
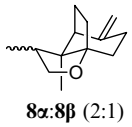
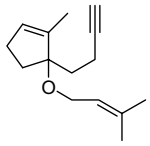
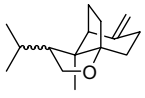
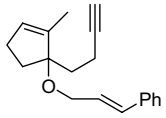
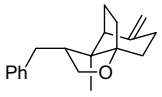
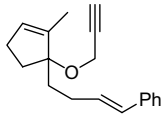
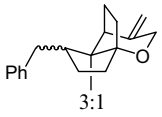
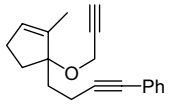
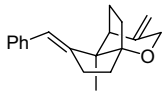
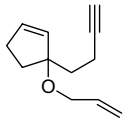
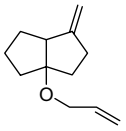
Table 1. Tandem radical cyclization to tricyclo[4.3.2.0^{1,5}]undecanes[5]



Entry	Substrate	Product[a] α:β[c]	Yield[b] (%)
1		 **8α:8β** (2:1)	89
2		 4:1	76
3		 α only	80
4		 3:1	60
5			61
6			64[d]

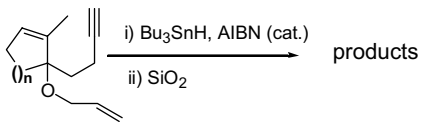
[a] The reaction conditions: the substrate was refluxed with Bu_3SnH (1.5 equiv) and AIBN (0.1 equiv) in benzene (0.01 M) for 2 h and the cooled reaction mixture was stirred with SiO_2 overnight.
[b] Isolated yield after column chromatography.
[c] The ratio was determined by ^1H NMR.
[d] The reaction concentration was 0.005 M.

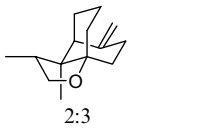
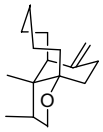
Lowering the concentration of the reaction to promote the rearrangement did not show any sign of the formation of the rearranged product. The result in entry 6 clearly supported the tandem radical cyclization–rearrangement–cyclization sequence as shown in Scheme 1 to form the tricyclic compounds. Since the substrate does not have the methyl group to stabilize the rearranged intermediate, the rearrangement did not occur and the reaction stopped after the first radical cyclization reaction and was quenched to form the diquinane structure.

With the successful construction of tricyclo[4.3.2.0^{1,5}]undecanes, we decided to explore the possibility of generalization of the reaction to construct tricyclo[4.3.*n*.0^{1,5}]alkanes since generalization of this tandem cyclization reaction for other ring sizes would include tricyclo[4.3.5.0^{1,5}]tetradecane system that could serve as the key intermediate for the synthesis of pleuromutiline.[7] Precursors for the cyclization were prepared from cyclic enones in the same way as for the substrates for the synthesis of tricyclo[4.3.2.0^{1,5}]undecanes. The cyclization reaction proceeded smoothly to produce the desired tricyclic compounds (Table 2).

Contrary to the tricyclo[4.3.2.0^{1,5}]undecanes where tandem radical cyclization reaction has exclusive preference toward one isomeric product of the ring skeleton, others could produce mixtures of skeletal isomers. When the ring size of the substrate was six ($n = 2$), a mixture of two skeletal isomers was obtained in equal amount. When the ring size of the substrate was larger than six, the skeletal isomer that was not found in the tricyclo[4.3.2.0^{1,5}]undecane became the sole isomeric product from the cyclization reaction. This unexpected selectivity could be due to the increasing steric interaction between the existing ring and the five-membered ring during the final cyclization sequence for the formation of the isomer like **8**. This result is also crucial for the applicability of the cyclization reaction to the total synthesis of pleuromutiline, as pleuromutiline has the same skeletal isomer as the

Table 2. Tandem radical cyclization to tricyclo[4.3.*n*.0^{1,5}]alkanes



n	Product[a,b]	Yield[c] (%)
2	 2:3	64
3	 **9**	80
4	 **10**	40

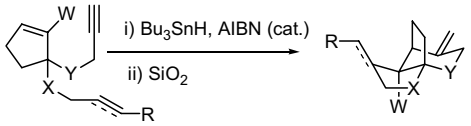
[a] The reaction conditions: the substrate was refluxed with Bu_3SnH (1.5 equiv) and AIBN (0.1 equiv) in benzene (0.01 M) for 2 h and the cooled reaction mixture was stirred with SiO_2 overnight.
[b] Relative stereochemistry was assigned through NOESY experiment.
[c] Isolated yield after column chromatography.

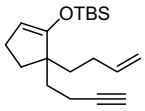
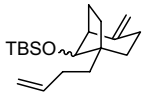
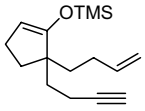
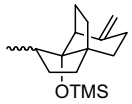
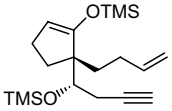
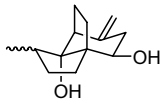
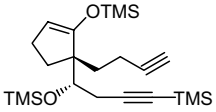
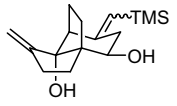
tricyclo[4.3.5.0^{1,5}]tetradecane compound **10** shown in Table 2.

Next we turned our attention to the formation of carbocyclic compounds. The precursors for the carbocyclic compounds were prepared through the same sequence as the preparation of the precursor for the radical cyclization in suberosenone synthesis. After direct butenylation or butynylation of 2-carboethoxy cyclopentanone, the ketone was protected as the corresponding acetal and the remaining ester was converted into the other required alkene or alkyne appendage for the tandem cyclization reaction (entries 3 and 4). For the substrates in entries 1 and 2, 2-carboethoxy cyclopentanone was alkylated twice as dianions, and the decarboxylation produced the corresponding cyclopentanone with proper appendages. The result of the radical cyclizaiton reaction was summarized in Table 3.

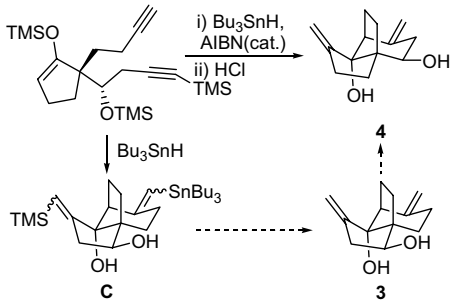
Though W could be any functional group capable of stabilizing the rearranged radical intermediate, the size of W also played an important role for the tandem cyclization as OTBS group blocked the second cyclization to form the tricyclic structure after the rearrangement (entry 1). When the OTMS group replaced the OTBS group, the tandem cyclization reaction proceeded smoothly (entries 2–4). Contrary to the expectation, the structure of the product in entry 4 was not the one we expected from the tandem radical cyclization involving the rearrangement. Since only the terminal alkyne can form the initial vinyl radical intermediate, the product should have been **3** with the hydroxyl group on the five-membered ring (Scheme 2).

Table 3. Tandem radical cyclization to tricyclo[4.3.2.0^{1,5}]undecanes



Entry	Substrate	Product[a] α:β[c]	Yield[b] (%)
1			64
2		 1:1	59
3		 1:1	55[d]
4		 1:1	60[d]

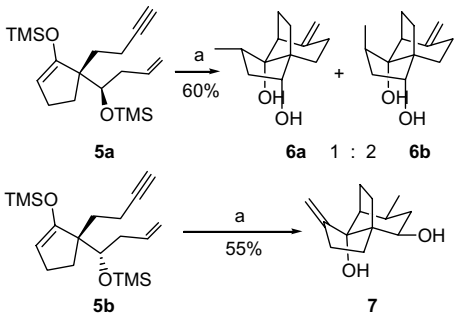
[a] The reaction conditions: the substrate was refluxed with Bu_3SnH (1.5 equiv) and AIBN (0.1 equiv) in benzene (0.01 M) for 2 h and the cooled reaction mixture was stirred with SiO_2 overnight.
[b] Isolated yield after column chromatography.
[c] The ratio was determined by ^1H NMR.
[d] The reaction mixture was treated with 1% HCl after the radical cyclization.



Scheme 2. Expected cyclization route to **3** and **4**.

The formation of **4** was initially rationalized by acid catalyzed rearrangement of **3** to **4**, as the tertiary alcohol of **3** could form an allylic cation easily and could undergo similar rearrangement as the cyclopropyl methyl radical rearrangement. However, a careful examination of the structure of **4** revealed that the stereochemistry of the alcohol on the tether might play an important role in forming **4** as the stereochemistry of the alcohol in the product was the more stable equatorial isomer. The equatorially positioned alcohol might have promoted the direct cyclization into the six-membered ring from the intermediate similar to **A**. To probe this possibility, we subjected **5a** and **5b** to the radical cyclization reaction separately. Two stereoisomers of the alcohol would provide the information on the effect of stereochemistry of the alcohol on the cyclization reaction. When **5a** and **5b** were subjected to the radical cyclization reaction condition, structurally different products were obtained (Scheme 3).[8]

In the reaction of **5a**, the anticipated product **6** was obtained following the radical cyclization–rearrangement–cyclization sequence. On the other hand, **5b** produced the unanticipated product **7** that was clearly the product of the tandem radical cyclization reaction without the rearrangement. While the hydroxyl group of **5a** was located at the axial position and showed 1,3-diaxial interaction with the other hydroxyl group that could not provide stabilization of the transition state for the direct cyclization, the hydroxyl group of **5b** was positioned at the equatorial position during the cyclization reaction to stabilize the six-membered ring transition state for the direct cyclization right after the first radical cyclization before the rearrangement could proceed. This result



Scheme 3. Reagents: (a) Bu_3SnH, AIBN; SiO_2.

also explained why **2** was the exclusive product from **1** during the total synthesis of subserosenone. When **1** reacted with the tin radical, the tin radical added to either of the two terminal alkynes to form two different intermediates. While one rearranged to form more stable radical intermediate before the second radical cyclization reaction, the other intermediate underwent the second radical cyclization reaction before the rearrangement. Then, both cyclization products eventually produced **2**. It became evident that addition of a substituent with the proper stereochemistry facilitated the cyclization reaction of the tether[9] and could alter the reaction pathway.

In conclusion, a reliable and general synthetic method to construct tricyclo[4.3.*n*.$0^{1,5}$]alkane skeleton was developed. It was clearly demonstrated that the reaction pathway could be different to form the tricyclic compounds depending on the presence and the stereochemistry of substituents in the tether.

Acknowledgements

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8. All the cyclization products gave satisfactory spectroscopic data for the structures. Spectral data of selected compounds; **4** ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.09 (t, 1H, J = 2.6 Hz), 5.04 (t, 1H, J = 2.2 Hz), 4.84 (m, 2H), 3.98 (m, 1H), 2.73 (d, 1H, J = 5.8 Hz), 2.68 (m, 1H), 2.54 (m, 1H), 2.49 (d, 1H, J = 6.3 Hz), 2.16 (m, 1H), 1.92 (ddd, 1H, J = 15.3, 10.3, 5.2 Hz), 1.78–1.69 (m, 3H), 1.55 (b s, 1H), 1.50 (b s, 1H), 1.37 (ddd, 1H, J = 14.6, 10.3, 4.3 Hz), 1.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 148.3, 111.0, 108.1, 86.9, 72.9, 55.4, 50.2, 37.3, 28.7, 28.6, 25.5, 24.7. IR (neat, cm^{-1}) 3411, 2944, 1651, 1086, 1041, 999, 892. HRMS: calcd for $C_{17}H_{24}O_3$: 206.1307, found: 206.1307. **6a** ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78 (t, 1H, J = 2.3 Hz), 4.70 (t, 1H, J = 2.3 Hz), 3.92 (m, 1H), 2.66 (d, 1H, J = 6.3 Hz), 2.52 (m, 1H), 2.36 (s, 1H), 2.34 (m, 1H), 2.22–2.15 (m, 2H), 2.01 (m, 1H), 1.85–1.76 (m, 2H), 1.66 (m, 1H), 1.56–1.45 (m, 2H), 1.28 (m, 1H), 1.05 (d, 3H, J = 7.7 Hz). ^{13}C NMR (100 MHz,

$CDCl_3$): δ 151.0, 110.4, 90.2, 77.8, 54.2, 52.0, 42.6, 41.1, 30.5, 27.8, 26.6, 25.7, 17.6. **6b** ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.54 (t, 1H, *J* = 2.3 Hz), 4.50 (t, 1H, *J* = 2.3 Hz), 3.88 (d, 1H, *J* = 3.8 Hz), 2.79 (m, 1H), 2.66 (t, 1H, *J* = 5.8 Hz), 2.39–2.31 (m, 2H), 2.24 (dd, 1H), 2.14 (m, 1H), 2.01 (dd, 1H, *J* = 14.2, 8.4 Hz), 1.68 (b, 1H), 1.58 (m, 1H), 1.47–1.38 (m, 3H), 1.26 (dd, 1H, *J* = 11.6, 3.0 Hz), 1.03 (d, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 104.5, 89.8, 76.8, 58.9, 45.9, 44.2, 42.9, 41.3, 40.6, 27.8, 27.7, 18.7. **7** ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03 (t, 1H, *J* = 2.6 Hz), 4.94 (t, 1H, *J* = 2.3 Hz), 3.97 (m, 1H), 2.63 (m, 1H), 2.50 (m, 1H), 2.36 (m, 1H), 1.87 (dd, 1H, *J* = 4.0, 2.1 Hz), 1.78–1.65 (m, 4H), 1.62 (m, 1H), 1.41 (m, 1H), 1.32 (m, 2H), 0.99 (m, 1H), 0.87 (d, 3H, *J* = 6.9 Hz), 0.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 106.8, 87.7, 72.3, 54.8, 45.0, 36.7, 28.7, 28.6, 28.5, 24.9, 19.7, 18.8. **8α** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.56 (t, 1H, *J* = 2.04 Hz), 4.50 (t, 1H, *J* = 2.04 Hz), 4.20 (t, 1H, *J* = 9.0 Hz), 3.44 (t, 1H, *J* = 9.0 Hz), 2.70 (t, 1H, *J* = 7.2 Hz), 2.54 (m, 1H), 2.36 (m, 1H),2.22 (dd, 1H, *J* = 14.1, 7.2 Hz), 1.97 (m, 2H), 1.81 (m, 2H), 1.18 (dd, 1H, *J* = 14.1, 2.0 Hz), 1.11 (m, 1H), 1.12 (s, 3H), 0.95 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.60, 106.80, 91.77, 73.21, 48.41, 45.16, 45.04, 43.68, 37.94, 31.25, 27.72, 25.74, 17.18, IR (neat, cm^{-1}) 2953, 2870, 2285, 1646, 1446, 1375, 1235, 1153, 1112, 1058, 1028, 949, 883. HRMS: calcd for $C_{13}H_{20}O$: 192.1514, found: 195.1525. **8β** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.59 (t, 1H, *J* = 2.08 Hz), 4.54 (t, 1H, *J* = 2.08 Hz), 4.12 (t, 1H, *J* = 8.6 Hz), 3.50 (t, 1H, *J* = 9.9 Hz), 2.52 (m, 1H), 2.49 (d, 1H, *J* = 6.0 Hz), 2.25 (m, 2H), 2.10 (m, 1H), 1.87 (m, 1H), 1.74–1.66 (m, 3H), 1.35 (m, 1H), 0.88 (d, 3H, *J* = 6.8 Hz), 0.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.74, 107.82, 90.54, 73.60, 51.33, 50.86, 36.92, 33.40, 31.33, 26.94, 25.49, 12.42, 11.88. IR (neat, cm^{-1}) 2959, 2874, 1775, 1720, 1684, 1644, 1471, 1380, 1339, 1194, 1151, 1084, 1062, 1009, 993, 907, 883 HRMS: calcd for $C_{13}H_{20}O$: 192.1514, found: 195.1525. **9** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.58 (m,2H), 3.90 (t, 1H, *J* = 8.7 Hz), 3.41 (dd, 1H, *J* = 9.8, 8.3 Hz), 2.57 (m, 2H), 2.39 (d, 1H, *J* = 9.8 Hz), 2.19 (m, 2H), 1.92 (m, 2H), 1.75 (m, 4H), 1.66 (m, 2H), 1.45 (m, 1H), 0.98 (s, 3H), 0.75 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.50, 108.25, 85.29, 71.01, 48.00, 45.33, 40.39, 37.78, 34.55, 30.92, 30.24, 26.56, 22.79, 15.64, 10.33 IR (neat, cm^{-1}) 2924, 2867, 1647, 1468, 1381, 1253, 1111, 1043, 1030, 1018, 958, 932, 885 HRMS: calcd for $C_{15}H_{24}O$: 220.1827, found: 220.1832. **10** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.82 (t, 1H, *J* = 2.3 Hz), 4.71 (t, 1H, *J* = 2.3 Hz), 3.82 (t, 1H, *J* = 8.7 Hz), 3.30 (dd, 1H, *J* = 9.8, 8.2 Hz), 2.66–2.55 (m, 2H), 2.43 (m, 1H), 2.29 (dd, 1H), 2.00–1.80 (m, 5H), 1.74–1.56 (m, 5H), 1.40 (m, 2H), 0.88 (s, 3H), 0.75 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.96, 111.78, 84.33, 68.80, 47.00, 45.09, 41.87, 38.36, 34.13, 33.17, 33.06, 29.31, 26.50, 26.09, 15.82, 10.88. IR (neat, cm^{-1}) 2922, 2859, 1641, 1465, 1452, 1434, 1384, 1264, 1235, 1196, 1128, 1088, 1035, 952, 925, 889. HRMS: calcd for $C_{16}H_{26}O$: 234.1984, found: 234.1986.

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