Notes

Syntheses of Concave-Shaped [5,5,5]-Tricyclic Triquinanes by Pd-Catalyzed Enediyne Cycloreduction

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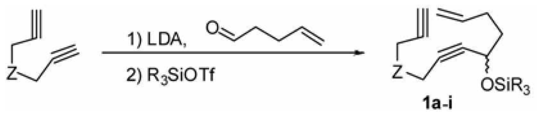
Pd-catalyzed enediyne cyclization gives a various polycyclic compounds in a very convenient single step. A few years ago, we reported a cascade cycloreduction of various enediynes leading to [m,5,n]-tricyclic compounds catalyzed by palladium catalysts[1] and, last year, we could synthesize Ceratopicanol by using this method as a key step.[2] This reaction proceeded with high levels of stereoselectivities leading to concave-shaped triquinane skeletons accompanying a significant increase in structural complexity.

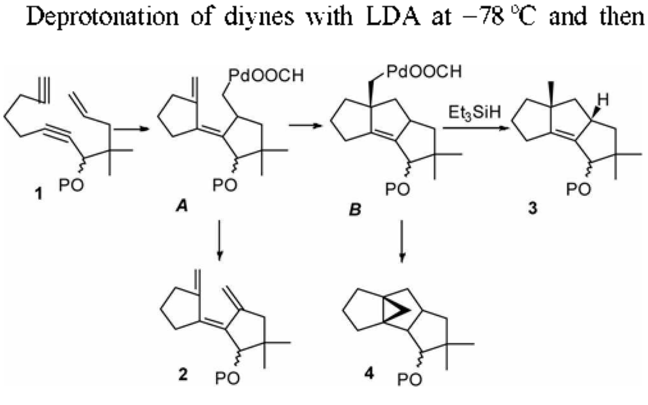
A major problem was found to arise from competition between β-elimination of the alkylpalladium intermediates ***A*** and carbopalladation of intermediate ***B*** which formed **4**, respectively (Scheme 1).[3] This problem could be overcome by changing the reaction conditions associated with mainly palladium catalysts and additives. Herein we wish to report a general entry to concave-shaped [5,5,5]-triquinane skeletons by employing Pd-catalyzed enediyne cycloreduction methodology.

Results and Discussion

First, various enediynes were prepared according to the well-known methods (eq. 1).



(1)



Scheme 1

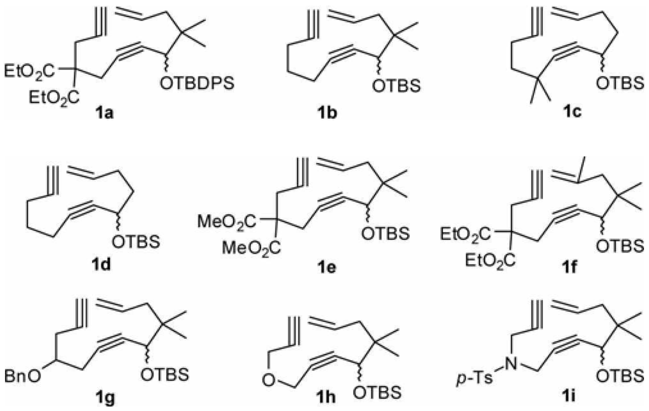


Figure 1

Deprotonation of diynes with LDA at −78 °C and then treatment of the corresponding aldehydes in THF gave the corresponding alcohols which were protected with trialkylsilyl trifluoromethanesulfonate to give our substrates **1a-i** in g-scales (Figure 1). In order to find optimal cycloreduction conditions leading to a general entry to [5,5,5]-tricyclic compounds, we first tested a substrate **1a** under different

Table 1. Cycloreduction of **1a** under Pd catalysis

	Pd catalyst (5 mol%) Additives (equiv)	Solvent	Temp (°C) Time (h)	**3a** (%yield)
1	[(π-allyl)PdCl]$_2$ PPh$_3$(0.1)/HCOOH (2)	DMF	80/2	70
2	Pd(PhCN)$_2$Cl$_2$	DMF	80/6	75
3	Pd(CH$_3$CN)$_2$Cl$_2$	DMF	80/8	Nr
4	Pd$_2$(dba)$_3$	DMF	80/4	58^a (**2a**)
5	Pd(OAc)$_2$	DMF	80/4	Dimer
6	Pd(PPh$_3$)$_4$	DMF	80/6	Dimer
7	2 mol% Pd(PhCN)$_2$Cl$_2$	DMF	100/4	63
8	Pd(PhCN)$_2$Cl$_2$	toluene	110/3	70
9	Pd(PhCN)$_2$Cl$_2$	EDC	70/2	47
10	Pd(PhCN)$_2$Cl$_2$	Dioxane	100/3	59
11	Pd(PhCN)$_2$Cl$_2$	CH$_3$CN	80/4	68
12	Pd(PhCN)$_2$Cl$_2$ HCOOH(2)/Et$_3$SiH(2)	DMF or dioxane	80/6	72-78

^{a}Isolated yield of triene **2a**.

conditions (Table 1).

We have utilized $[(\pi\text{-allyl})PdCl]_2$, $Pd(CH_3CN)_2Cl_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, and $Pd(PhCN)_2Cl_2$ as Pd-precatalysts for cycloreduction of **1a** using two equivalent of HCOOH as a reductant and DMF as a solvent (entries 1-6). Among these, $[(\pi\text{-allyl})PdCl]_2$ and $Pd(PhCN)_2Cl_2$ successfully catalyzed **1a** to afford the corresponding product **3a** in 70% and 75% yields, respectively. $Pd(CH_3CN)_2Cl_2$, even similar to $Pd(PhCN)_2Cl_2$, did not catalyze this reaction. $Pd_2(dba)_3$ catalyzed this reaction but afforded to the triene compound **2a** as a major product. Finally, when we employed $Pd(OAc)_2$ and $Pd(PPh_3)_4$ as catalysts, the unexpected dimerized product was obtained exclusively. Completion of this sequential cyclization catalyzed by Pd compound required increased stability and fast reduction of the Pd-alkyl intermediate. The decreased amount of precatalyst from 5 mol% to 2 mol% was less effective in terms of isolated yield of **3** (entry 7). Use of nonpolar solvents such as toluene, EDC, dioxane, and acetonitrile were inferior to DMF (entries 8-11). To facilitate formation of **3**, stronger reductant might be required to cleave the carbon-Pd bond of ***B*** as soon as it was formed. Otherwise, triene **2** and further cyclized product **4** were formed. Triethylsilane turned out to be a good choice for this rapid reduction of alkylpalladium intermediate over unwanted β-elimination (entry 12). Thus, an optimal condition for this cycloreduction was found: 5 mol% $Pd(PhCN)_2Cl_2$, 2 equivalents of HCOOH and Et_3SiH in DMF or dioxane. This condition was applied to the structurally diverse enediynes **1b-1i** (Figure 2).

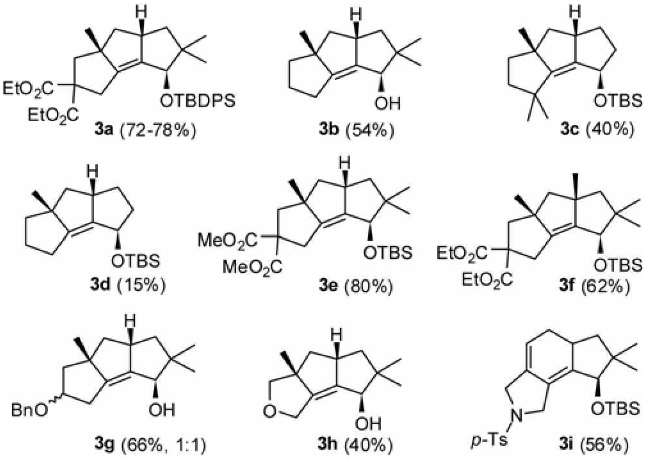


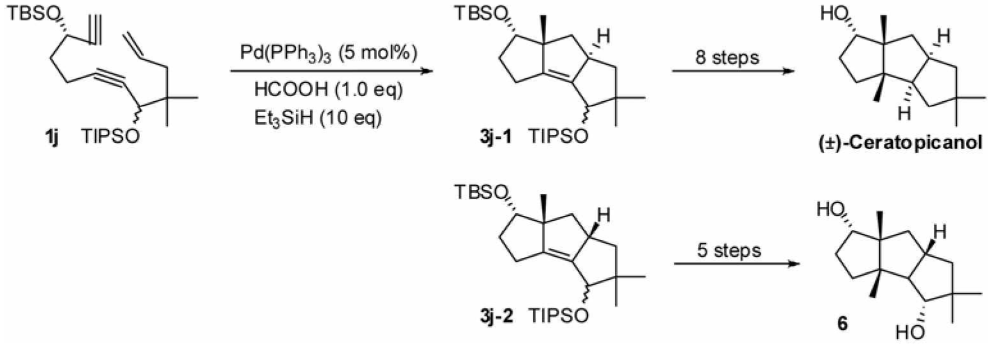
Figure 2

While **1b** and **1c** possessing a geminal dimethyl group gave the desired product **3b** and **3c** in 54% and 40% yields, respectively. **1d** with no geminal alkyl group was less reactive to give **3d** in only 15% yield. The substrate **1e** has the same carbon skeleton as **1a** but has different protecting groups. The cycloreduction of **1e** was virtually similar to that of **1a** to give **3e** in 80% yield. The **1f**, a homolog of **1a** having a methyl substituent on the olefinic position, also gave the cycloreduced product **3f** in 62% yield under our conditions. The substrate **1g** was designed for application of its cycloreduced product. Cycloreduction of **1g** under our conditions gave about 1:1 mixture of two isomeric products **3g** in 66% yield. Both isomers **3g-1** and **3g-2** could be separated by HPLC chromatography. Finally, this method was applied two enediynes bearing a heteroatom linker. The oxygen-linkered **1h** was also cycloreduced to give **3h** in 40% yield, while the nitrogen-linkered **1i** was not cycloreduced to **3i** but cycloisomerized to give **3i** in 56% yield. Note that some products **3b**, **3g**, and **3h** were desilylated by adding 1.0 M solution of tetrabutylammonium fluoride solution in THF.

Stereochemistries of **3a-h** were speculated based on 2D NMR of **3j-2** and X-ray study of **6**, which were intermediates to the ceratopicanol synthesis (Scheme 2).[2]

A catalytic mixture of $[(\pi\text{-allyl})PdCl]_2$ (5 mol%), PPh_3 (20 mol%), HCOOH (1.0 eq), and triethylsilane (10 eq) in 1,4-dioxane was found to transform enediyne **1j** to the cycloreduced tricycle **3j** in 70-75% yield (α/β ratio of angular H = 1/3) along with only a little amount of the triene.[4] Stereoselectivity in our cycloreduction was turned out that the present cycloreduction was highly stereoselective having concave-relationship among three fused 5-membered rings. Both **3j-1** and **3j-2** could be transformed to (±)-ceratopicanol.

In conclusion, we have shown a general entry to fused [5,5,5] tricyclic compounds with concave shapes starting from the corresponding linear enediynes substrates under mild Pd catalysis.[5]



Scheme 2

Experimentals

General experimental procedure (**3a-h**): A mixture of enediyne **1a-h** (0.4 mmol), Pd (5 mol%), PPh_3 (10 mol%). HCOOH (0.8 mmol). triethylsilane (0.8 mmol) and dried solvent(1.0 mL) in a 5 mL test tube was heated at 80°C-100°C for 2-24 h under argon atmosphere. The reaction was monitored by checking TLC periodically. Upon completion. the solvent was removed under vacuum and the crude product was subjected for flash column chromatography to afford the corresponding products **3a-h** in fair to good yields as shown in Figure 2. **3a**: IR (NaCl. cm^{-1}) 2932. 2858, 1733. 1472; ^1H NMR (400 MHz. $CDCl_3$) δ 7.68-7.64 (m. 4H), 7.44-7.31 (m. 6H). 4.20-3.94 (m. 4H). 3.85 (s. 1H). 3.54 (m. 1H). 2.19 (d. J = 13.6 Hz. 1H). 2.18 (dd. J = 16.4. 1.6 Hz. 1H). 2.13 (dd. J = 12.0. 4.4 Hz. 1H). 2.06 (dd. J = 11.6. 6.4 Hz. 1H). 1.93 (d. J = 13.6 Hz. 1H). 1.87 (dd. J = 11.2. 2.0 Hz. 1H). 1.43 (dd. J = 11.2. 9.2 Hz. 1H). 1.21 (t. J = 7.2 Hz. 3H). 1.14 (s. 3H). 1.12 (t. J = 7.2 Hz. 3H). 1.04 (s. 9H). 1.00 (dd. J = 11.2. 4.6 Hz. 1H). 0.90 (s. 3H). 0.75 (s. 3H); ^{13}C NMR (100 MHz. $CDCl_3$) δ 172.21. 172.12. 145.04. 141.70. 136.00. 134.43. 134.22. 129.37. 129.25. 127.43. 127.21. 77.13. 61.57. 61.34. 61.30. 59.04. 52.62. 50.23. 46.53. 46.26. 42.94. 31.54. 28.65. 26.98. 24.36. 23.77. 19.57. 14.01. 13.90; HRMS calculated for $C_{36}H_{48}O_5SiNa^+$ 611.3169; found. 611.3165. **3b**: IR (NaCl. cm^{-1}) 3356, 2949, 2861; ^1H NMR (400 MHz. $CDCl_3$) δ 3.92 (s. 1H), 3.63 (m, 1H). 2.24-2.13 (m. 2H). 2.10 (dd. J = 12.0. 6.4 Hz. 1H). 2.05-1.97 (m. 1H). 1.92-1.83 (m. 1H). 1.76 (dd. J = 12.8. 9.2 Hz. 1H). 1.58-1.53 (m. 1H). 1.42-1.37 (m. 3H). 1.12 (s. 3H). 1.05 (s. 3H). 1.03 (dd. J = 12.4. 6.8 Hz. 1H). 0.96 (s. 3H); ^{13}C NMR (100 MHz. $CDCl_3$): δ 151.75. 139.69. 76.61. 60,60, 51.93. 50.58. 46.25. 44.11. 39.48. 28.70. 26.49. 23.05. 22.62. 22.39; HRMS calculated for $C_{14}H_{22}ONa^+$ 229.1568; found. 229.1559. **3c**: IR (NaCl. cm^{-1}) 2955, 2931. 2859, 1472; ^1H NMR (400 MHz. $CDCl_3$) δ 4.71 (t. J = 5.6 Hz. 1H). 3.51 (m. 1H), 2.13-2.06 (m. 1H). 2.00-1.87 (m. 3H). 1.78-1.66 (m. 2H). 1.53-1.43 (m. 2H). 1.19 (s. 6H). 1.16 (s. 3H). 1.03-0.97 (m. 2H). 0.88 (s. 9H). 0.08 (s. 3H). 0.07 (s. 3H); ^{13}C NMR (100 MHz. $CDCl_3$) δ 155.69, 139.86, 68.26. 63.39, 52.56. 51.44, 44.43. 39.91. 38.35. 36.83. 30.08. 29.82. 27.77. 25.94. 23.25. 18.00. −4.09. −4.37; HRMS calculated for $C_{20}H_{36}OSiNa^+$ 343.2433; found. 343.2429. **3d**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.28 (t. J = 4.8 Hz, 1H), 2.46 (m, 1H). 2.22-2.14 (m. 3H). 2.06-1.94 (m. 4H). 1.84-1.74 (m. 3H). 1.60-1.56 (m. 1H). 1.26 (s. 3H). 1.13-1.06 (m. 1H). 0.83 (s. 9H). 0.04 (s. 3H). 0.03 (s. 3H); HRMS calculated for $C_{18}H_{32}OSiNa^+$ 315.2120; found. 315.2126. **3e**: IR (NaCl. cm^{-1}) 2954. 2930, 2895. 2858, 1738. 1435; ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (s. 3H). 3.71 (s. 1H). 3.69 (s, 3H). 3.50 (m. 1H), 2.86 (m. 2H), 2.37 (d. J = 14.0 Hz. 1H). 2.12 (dd. J = 11.2. 6.0 Hz. 1H). 2.08 (d. J = 13.6 Hz. 1H). 1.76 (dd. J = 12.8. 10.0 Hz. 1H). 1.51 (dd. J = 11.2. 9.6 Hz. 1H). 1.11 (s. 3H). 1.00 (s. 3H). 0.96 (dd. J = 8.8. 4.6 Hz. 1H). 0.86 (s. 9H). 0.80 (s. 3H). 0.04 (s. 3H). 0.00 (s. 3H); ^{13}C NMR (100 MHz. $CDCl_3$) δ 172.76. 172.61. 143.57. 143.27. 76.37, 61.78, 59.11, 52.85. 52.78, 50.19. 46.44, 46.18, 42.59. 32.17, 28.67, 26.14. 25.77. 23.88. 23.73. 18.20. −4.33. −5.07; HRMS calculated for: $C_{24}H_{40}O_5SiNa^-$ 459.2543; found. 459.2548. **3f**: IR (NaCl. cm^{-1}) 2956, 2930, 2858, 1735, 1475; ^1H NMR (400 MHz. $CDCl_3$) δ 4.26-4.11 (m, 4H). 3.69 (s. 1H), 2.69 (d. J = 16.4 Hz. 1H). 2.79 (d. J = 16.4 Hz. 1H). 2.32 (d. J = 13.6 Hz. 1H). 2.10 (d. J = 13.6 Hz. 1H). 1.89 (s. 2H). 1.49-1.46 (m. 2H). 1.35 (s. 3H). 1.28-1.24 (m. 6H). 1.20 (s. 3H). 1.02 (s. 3H). 0.88 (s. 9H). 0.80 (s. 3H). 0.05 (s. 3H). 0.01 (s. 3H); ^{13}C NMR (100 MHz. $CDCl_3$) δ 172.68, 172.46. 145.48, 143.33. 77.13. 61.63. 61.57. 61.40. 59.92. 59.06. 58.15. 53.78. 49.06. 45.42. 31.56. 31.46. 29.69. 29.22. 25.83. 24.70. 18.24. 14.03. 13.98. −4.30. −5.21; HRMS calculated for $C_{27}H_{46}O_5SiNa^-$ 501.3012; found. 501.3018. **3g-1**: IR (NaCl. cm^{-1}) 3419, 3031, 2927, 2862, 1454; ^1H NMR (400 MHz. $CDCl_3$) δ 7.36-7.27 (m. 5H), 4.49 (s, 2H). 4.14-4.08 (m, 1H). 3.91 (d. J = 4.4 Hz. 1H). 3.51 (m. 1H). 2.70 (ddd. J = 15.4. 6.4. 1.2 Hz. 1H). 2.25 (dt. J = 16.4. 5.4 Hz. 1H). 2.13 (dd. J = 11.6. 6.4 Hz. 1H). 1.82-1.72 (m. 2H). 1.71 (d. J = 4.4 Hz. 1H). 1.35 (dd. J = 11.6. 6.4 Hz. 2H). 1.26 (s. 3H). 1.05 (s. 3H). 1.00 (dd. J = 12.4. 6.8 Hz. 1H). 0.93 (s. 3H); ^{13}C NMR (100 MHz. $CDCl_3$) δ 147.64, 142.29. 138.59, 128.34. 127.57. 127.46. 81.42. 76.40. 71.08. 58.10. 53.03. 48.87. 46.18. 45.74. 43.84. 31.47. 28.70. 25.02. 22.57; HRMS calculated for $C_{21}H_{28}O_2K^-$ 351.1726; found. 351.1728. **3g-2**: IR (NaCl. cm^{-1}) 3419. 2960, 2861, 1715, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H). 4.48 (ABq. $\Delta\delta$ = 4.4 Hz. J = 12.0 Hz, 2H), 4.38 (m, 1H), 3.95 (s, 1H). 3.59 (m, 1H). 2.56 (ddd. J = 17.2. 8.0. 4.4 Hz. 1H). 2.33 (ddd. J = 17.2. 4.8. 2.4 Hz. 1H). 2.09 (dd. J = 11.6. 6.0 Hz. 1H). 2.02 (dd. J = 12.8. 6.4 Hz. 1H). 1.77 (dd. J = 12.8. 8.8 Hz. 1H). 1.52 (dd. J = 11.6. 6.0 Hz. 1H). 1.34 (m. 1H). 1.25 (s. 1H). 1.10 (s. 3H). 1.04 (s. 3H). 1.07-1.02 (m. 1H). 0.99 (s. 3H); ^{13}C NMR (100 MHz. $CDCl_3$) δ 147.88, 141.46. 138.52. 128.33. 127.61. 127.48. 82.34. 76.57. 71.12. 59.30. 52.03. 49.74. 46.87. 46.45. 44.04. 30.17. 28.61. 23.93. 22.60; HRMS calculated for $C_{21}H_{28}O_2Na^-$ 335.1987; found. 335.1991. **3h**: IR (NaCl. cm^{-1}) 3419, 2952, 2862. 1456; ^1H NMR (400 MHz. $CDCl_3$) δ 4.32-4.22 (m, 2H). 3.94 (d. J = 4.8 Hz. 1H). 3.81 (m. 1H). 3.71 (d. J = 8.0 Hz. 1H). 3.39 (d. J = 8.0 Hz. 1H). 2.06 (dd. J = 11.6. 6.0 Hz. 1H). 1.81 (dd. J = 12.8. 9.2 Hz. 1H). 1.54 (dd. J = 11.6. 9.2 Hz. 1H). 1.43 (d. J = 4.8 Hz. 1H). 1.28 (s. 3H). 1.11 (dd. J = 12.8. 7.2 Hz. 1H). 1.06 (s. 3H). 1.01 (s. 3H); ^{13}C NMR (100 MHz. $CDCl_3$) δ 146.56. 141.28, 79.39, 76.22, 63.20, 61.67, 52.55, 47.65, 46.68, 43.54, 28.53. 22.41. 21.64; HRMS calculated for $C_{13}H_{20}O_2K^-$ 247.1100; found. 247.1114. **3i**: IR (NaCl. cm^{-1}) 2956. 2929. 2857. 1347; ^1H NMR (400 MHz. $CDCl_3$) δ 7.77-7.70 (m. 2H), 7.32-7.29 (m. 2H), 4.31 (bs, 1H), 4.24-3.97 (m, 4H). 2.43 (s. 3H), 2.26-2.14 (m. 5H), 2.02 (d. J = 16.0 Hz. 1H). 1.07 (s. 3H). 0.94 (s. 3H). 0.91 (s. 9H). 0.10 (s. 3H). 0.08 (s. 3H); ^{13}C NMR (100 MHz. $CDCl_3$) δ 143.23. 138.49, 134.27, 130.87, 129.68. 127.91. 127.54, 127.25, 84.13, 56.05, 54.31. 49.27. 42.93. 28.39, 26.19, 24.24. 23.93. 21.49. 21.26. 18.27. −2.63. −4.12; HRMS calculated for $C_{26}H_{39}NO_3SSiNa^-$ 496.2318; found. 496.2322.

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