Revised

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Intramolecular Diels-Alder Reactions Employing Hydroxamate Tethers: The First Examples and Promising Prospects

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For references to other "temporary heteroatom tether strategies for intramolecular Diels-Alder reactions, see: for silicon, (a) Sieburth, S. M.; Lang, J. *J. Org. Chem.* **1999**, *64*, 1780–1781 and references therein, for boron, (b) Batey, R. A; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450–451 and references therein, for magnesium and aluminum, (c) Bertozzi, F.; Olsson, R.; Frejd, T. *Org. Lett.* **2000**, *2*, 1283–1286 and references therein., for esters, (d) Kim, P.; Nantz, M. H.; Kurth, M. J.; Olmstead, M. M. *Org. Lett.* **2000**, *2*, 1831–1834 and references therein, for amides, (e) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170–5180 and references therein, for carbamates and ureas, (f) Kraus, G. A.; Gougie, D.; Jacobson, R. A.; Su, Y. Y. *J. Org. Chem.* **1989**, *54*, 2425–2428 and references therein, and for sulfonates, see: (g) Metz, P. *J. prakt. Chem.* **1998**, *340*, 1–10 and references therein.

Experimental section

Instrumentation. IR spectra ware recorded on a Horiba Fourier transform infrared spectrophotometer Model FT-210 instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded

on a Varian VXR-500 (500 MHz for ^1H and 125 MHz for ^{13}C), Varian Mercury-300 (300 MHz for ^1H and 75 MHz for ^{13}C) or Varian Gemini-200 (200 MHz for ^1H and 50 MHz for ^{13}C) instrument. The chemical shifts are given in δ unit relative to internal $CHCl_3$ (7.26 ppm for ^1H) or $CDCl_3$ (77 ppm for ^{13}C). All NMR experiments were performed using deuteriochloroform as a solvent unless otherwise indicated. Mass spectra were obtained on a JEOL JMS-DX303 instrument relying on a JMA-DA5000 mass data system. Elemental analyses were made with a Perkin-Elmer 2400 CHN Elemental Analyzer.

Analytical Procedure and Data Presentation. Analytical thin layer chromatography was performed on Merck precoated silica gel 60 F-254 (0.25 mm thickness). ^1H NMR spectral data were indicated in the form: δ value of signal (peak multiplicity, integrated number of protons and coupling constant (if any)). Splitting patterns are abbreviated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad.

General Reaction Procedure. All reactions, unless otherwise noted, were conducted under a nitrogen or an argon atmosphere. Liquid reagents were transferred via a dry hypodermic syringe from sure seal bottles to a reaction flask through a rubber septum wired on to the reaction flask. The septum can also serve to permit evacuation to eliminate air and introduce the inert gas by means of a steady stream of inert gas flowing system. Organic extracts were concentrated by evaporation with a rotary evaporator evacuated at around 60 mmHg. Column chromatography, unless otherwise specified, was performed on a Merck silica gel 60 7734 using an appropriate ratio of ethyl acetate (AcOEt)/hexane mixed solvent and abbreviated as CC.

Materials. Unless otherwise noted, materials were obtained from commercial suppliers and reagent grade materials were used without further purification. Toluene and benzene were freshly distilled from CaH_2 prior to use. Tetrahydrofuran (THF) was distilled from benzophenone/ketyl prior to use.

General procedure for the synthesis of hydroxamate-tethered trienes

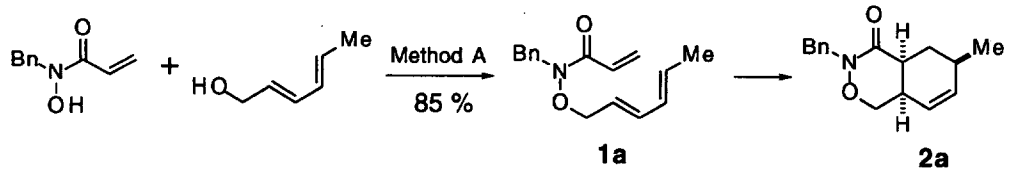
Method A: To a solution of hydroxamic acids (**5** or **7**) (4 mmol), allylic alcohols (**6** or **8**) (4.5 mmol), and triphenylphosphine (4.5 mmol) in THF (10 mL) was added dropwise

diethyl azodicarboxylate (DEAD) (4.5 mmol) at 0 °C. The mixture was stirred at room temperature for 1—4 h. The reaction was monitored by TLC analysis. The mixture was quenched with water and extracted with AcOEt. The combined organic layers were dried over Na_2SO_4 and evaporated to give a crude oil, which was purified by CC to give hydroxamate-tethered trienes.

Method B: To a solution of a hydroxamic acids (**5** or **7**) (4 mmol), allylic alcohols (**6** or **8**) (4.5 mmol) and tributylphosphine (4.5 mmol) in benzene (10 mL) was added 1,1'-(azodicarbonyl)dipiperidine (4.5 mmol) at 0 °C. The mixture was stirred at room temperature. The reaction was monitored by TLC analysis. The mixture was filtered through a pad of celite using hexane-AcOEt mixed solvent, and the filtrate was evaporated to give a crude oil, which was purified by CC to give hydroxamate-tethered trienes.

General procedure for thermal Diels-Alder Reaction of hydroxamate-tethered trienes

Hydroxamate-tethered trienes (0.2 mmol) were dissolved in toluene (2 mL). The solution was stirred at elevated temperature for several hours. The reaction was monitored by TLC analysis, and the reaction conditions were indicated in the text. The mixture was evaporated to give a crude oil, which was purified by CC to give cycloadducts.



1a **2a**

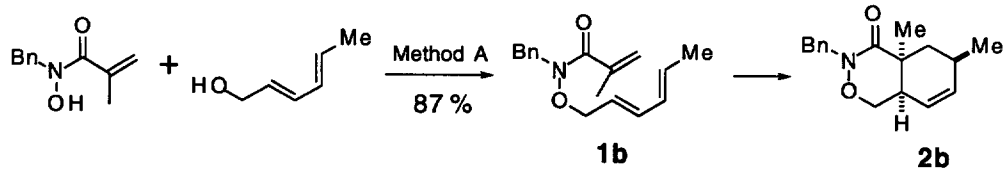
(2*E*,4*E*)-Hexadienyl *N*-benzyl-propenoylhydroxamate (1a).

^{1}H NMR (500MHz) δ 1.62 (s, 3H), 1.76 (d, 3H, J = 6.6 Hz), 4.26 (d, 2H, J = 6.6 Hz), 4.86 (s, 2H), 5.50–5.59 (m, 1H), 5.70–5.50 (m, 3H), 5.98–6.05 (m, 1H), 6.15 (dd, 1H, J = 10.3, 15.3 Hz), 6.57 (dd, 1H, J = 2.1, 17.1 Hz), 6.77 (dd, 1H, J = 10.3 17.1 Hz), 7.22–7.40 (m, 5H); ^{13}C NMR (50 MHz) δ 18.2, 52.3, 75.4, 17.9, 123.0, 127.7, 128.4, 128.6, 130.1, 131.4, 136.8, 136.9, 140.1, 171.7; IR (neat) 2926, 1660, 1452 cm^{-1}.

Cycloadduct (2a)

^{1}H NMR (500 MHz) δ 1.01 (d, 3H, J = 6,4 Hz, Me), 1.25–1.35 (m, 1H), 2.22–2.33 (m, 2H), 2.70–2.81 (m, 2H), 3.67 (dd, 1H, J = 9.2, 11.3 Hz), 3.98 (dd, 1H, J = 4.9, 11.3 Hz), 4.68 and

4.93 (ABq, 2H, J = 15.0 Hz), 5.40–5.44 (m, 1H), 5.73 (d, 1H, J = 9.8 Hz), 7.25–7.38 (m, 5H, ArH); ^{13}C NMR (50 MHz) δ 21.2, 30.3, 32.7, 34.3, 39.1, 50.1, 71.7, 122.8, 127.6, 128.1, 128.5, 136.2, 136.9, 170.1; IR (neat) 1676, 1430, 1240 cm^{-1}; exact mass, m/z 257.1419 (calcd for $C_{16}H_{19}NO_2$ m/z 257.1416). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.36. Found: C, 74.55; H, 7.44.

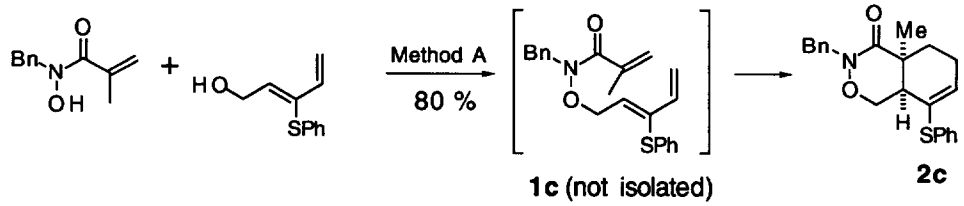


(2*E*,4*E*)-Hexadienyl *N*-benzyl-(2-methylpropenoyl)hydroxamate (1b).

^{1}H NMR (500 MHz) δ 1.76 (d, 3H, J = 6.7 Hz), 1.98 (s, 3H), 4.21 (d, 2H, J = 7.0 Hz), 4.82 (s, 2H), 5.26–5.29 (m, 1H), 5.34–5.36 (m, 1H), 5.49 (dd, 1H, J = 7.0, 15.0 Hz), 5.73 (dq, 1H, J = 15.0 Hz, J = 6.7 Hz), 6.05 (ddd, 1H, J = 1.5, 10.4, 15.0 Hz), 6.15 (dd, 1H, J = 10.4, 15.0 Hz), 7.25–7.40 (m, 5H); ^{13}C NMR (50 MHz) δ 18.1, 19.9, 51.3, 75.6, 17.7, 122.7, 127.6, 128.1, 128.5, 130.3, 131.9, 136.3, 136.5, 140.2, 171.6; IR (neat) 2926, 1657, 1454 cm^{-1}.

Cycloadduct (2b)

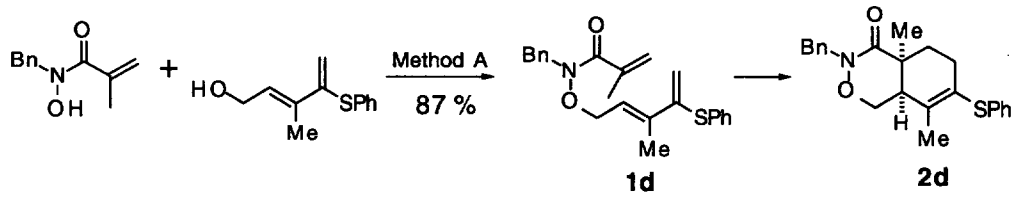
^{1}H NMR (500 MHz) δ 1.00 (d, 3H, J = 7.1 Hz), 1.28 (s, 3H), 1.24–1.30 (m, 1H), 2.04 (dd, 1H, J = 5.2, 11.5 Hz), 2.22–2.34 (m, 1H), 2.43–2.49 (m, 1H), 3.67 (dd, 1H, J = 9.7, 11.5 Hz), 4.00 (dd, 1H, J = 4.9, 11.5 Hz), 4.64 and 4.90 (ABq, 2H, J = 15.3 Hz), 5.36–5.42 (m, 1H), 5.66–5.72 (m, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR (50 MHz) δ 20.9, 22.0, 26.7, 38.0, 39.7, 41.6, 50.3, 72.4, 122.2, 127.5, 128.1, 135.5, 136.4, 173.2; IR (neat) 2958, 1654, 1242 cm^{-1}; exact mass, m/z 271.1566 (calcd for $C_{17}H_{21}NO_2$ m/z 271.1572).



Cycloadduct (2c)

^{1}H NMR (300 MHz) δ 1.29 (s, 3H), 1.76 (dt, 1H, J = 4.7, 13.5 Hz), 1.95–2.50 (m, 4H), 4.02 (dd, 1H, J = 7.7, 11.8 Hz), 4.24 (dd, 1H, J = 4.9, 11.8 Hz), 4.70 and 4.80 (ABq, 2H, J = 15.1 Hz), 6.26 (bt, 1H, J = 3.3 Hz), 7.18–7.40 (m, 10H); ^{13}C NMR (50 MHz) δ 22.4, 23.3, 29.0,

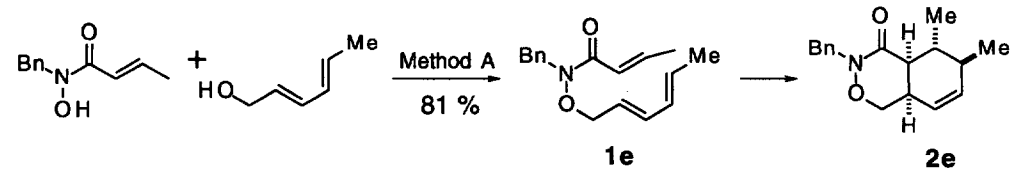
40.8, 44.3, 50.3, 71.8, 126.9, 127.6, 128.1, 128.5, 129.1, 129.5, 130.0, 134.2, 136.2 (2C), 172.4; IR (neat) 2960, 1656, 1242 cm^{-1}; exact mass, m/z 365.1452 (calcd for $C_{22}H_{23}NO_2S$ m/z 365.1449).



3-Methyl-4-phenylthio-(2*E*,4)-pentadienyl *N*-benzyl-(2-methylpropenoyl)hydroxamate (1d). ^1H NMR (300 MHz) δ 1.98 (s, 3H), 2.10 (s, 3H), 4.20 (d, 2H, *J* = 7.0 Hz), 4.81 (s, 2H), 5.26–5.29 (m, 2H), 5.34–5.36 (m, 3H), 7.25–7.40 (m, 10H); ^{13}C NMR (75 MHz) δ 21.7, 24.2, 50.4, 71.1, 120.1, 126.1, 126.3, 127.4, 127.6, 127.9, 128.0, 128.3, 128.5, 128.9, 129.5, 134.7, 134.9, 136.2, 174.3; IR (neat) 3030, 1690, 1240 cm^{-1}.

Cycloadduct (2d)

^1H NMR (300 MHz) δ 1.34 (s, 3H), 1.62–1.76 (m, 1H), 1.94 (s, 3H), 2.02–2.22 (m, 3H), 2.50–2.60 (m, 1H), 3.94 (dd, 1H, *J* = 7.4, 11.8 Hz), 4.25 (dd, 1H, *J* = 4.7, 11.8 Hz), 4.78 and 4.84 (ABq, 2H, *J* = 15.1 Hz), 7.15–7.40 (m, 10H); ^{13}C NMR (75 MHz) δ 19.9, 24.0, 27.9, 31.5, 40.2, 48.5, 50.3, 71.0, 126.1, 127.6, 127.9, 128.0, 128.5, 128.9, 129.5, 134.7, 134.9, 136.2, 172.3; IR (neat) 2960, 1657, 1240 cm^{-1}; Anal. Calcd for $C_{23}H_{25}NO_2S$: C, 72.79; H, 6.64. Found: C, 72.65; H, 6.81.

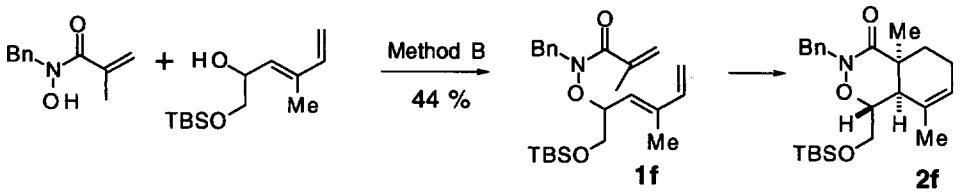


(2*E*,4*E*)-Hexadienyl *N*-benzyl-[(2*E*)-butenoyl]hydroxamate (1e).

^1H NMR (500 MHz) δ 1.76 (d, 3H, *J* = 6.7 Hz), 1.91 (d, 3H, *J* = 7.0 Hz), 4.27 (d, 2H, *J* = 7.0 Hz), 4.85 (s, 2H), 5.55 (dt, 1H, *J*= 15.0, 7.0 Hz), 5.75 (dq, 1H, *J* = 15.0, 6.7 Hz), 5.99–6.06 (m, 1H), 6.16 (dd, 1H, *J* = 10.4, 15.0 Hz), 6.46 (d, 1H, *J* = 15.3 Hz), 7.05 (dq, 1H, *J* = 15.3, 7.0 Hz), 7.23–7.35 (m, 5H); ^{13}C NMR (50 MHz) δ 18.1, 18.3, 50.3, 76.0, 120.6, 122.4, 127.5, 128.4, 130.3, 132.1, 136.6, 167.3; IR (neat) 2933, 1662, 1124 cm^{-1}.

Cycloadduct (2e)

^{1}H NMR (500 MHz) δ 1.02 (d, 3H, J = 7.3 Hz), 1.08 (d, 3H, J = 7.3 Hz), 1.77–1.83 (m, 1H), 1.85–1.95 (m, 1H), 2.42–2.50 (m, 1H), 2.72–2.78 (m, 1H), 3.80 (dd, 1H, J = 4.3, 11.0 Hz), 3.96 (dd, 1H, J = 11.0, 18.5 Hz), 4.76 and 4.80 (ABq, 2H, J = 15.1 Hz), 5.48–5.68 (m, 2H), 7.25–7.38 (m, 5H); ^{13}C NMR (50 MHz) δ 18.0, 20.1, 34.4, 36.5, 46.7, 49.8, 74.9, 124.9, 127.7, 128.4, 128.5, 134.8, 136.2, 171.9; IR (neat) 2960, 1650, 1245 cm^{-1}; exact mass, m/z 271.1581 (calcd for $C_{17}H_{21}NO_2$ m/z 271.1572).

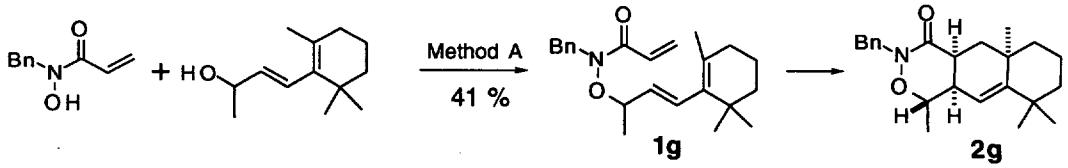


1-(*tert*-Butyldimethylsilyloxy)methyl-3-methyl-(2*E*,4)-pentadienyl *N*-benzyl-(2-methyl-propenoyl)hydroxamate (1f).

^{1}H NMR (500 MHz) δ –0.006 (s, 6H), 0.85 (s, 9H), 1.72 (s, 3H), 1.92 (s, 3H), 3.62 (dd, 2H, J = 4.2, 10.9 Hz), 4.78 and 4.84 (ABq, 2H, J = 15.4 Hz), 4.76–4.84 (m, 1H), 5.10 (d, 1H, J = 11.0 Hz), 5.24 (d, 1H, J = 17.4 Hz), 5.26–5.34 (m, 2H), 5.40 (d, 1H, J = 9.8 Hz), 6.32 (dd, 1H, J = 11.0, 17.4 Hz), 7.30–7.35 (m, 5H); ^{13}C NMR (50 MHz) δ –5.23, 12.6, 18.4, 19.9, 25.9, 51.3, 63.6, 71.2, 117.7, 122.8, 127.6, 128.2, 128.6, 129.8, 132.9, 136.4, 139.6, 140.3, 171.7; IR (neat) 2930, 1658, 1460 cm^{-1}.

Cycloadduct (2f)

^{1}H NMR (500 MHz) δ –0.026 (s, 3H), -0.031 (s, 3H), 0.88 (s, 9H), 1.22 (s, 3H), 1.36–1.42 (m, 1H), 1.61 (s, 3H), 1.84–1.93 (m, 1H), 1.95–2.06 (m, 1H), 2.10–2.18 (m, 2H), 3.56 (dd, 1H, J = 4.0, 11.5 Hz), 3.68 (dd, 1H, J = 7.8, 11.5 Hz), 3.86 (ddd, 1H, J = 4.0, 5.2, 7.8 Hz), 4.50 and 5.50 (ABq, 2H, J = 15.0 Hz), 5.47–5.51 (m, 1H), 7.23–7.33 (m, 5H); ^{13}C NMR (50 MHz) δ –5.41, 18.2, 21.4, 22.3, 22.7, 25.8, 28.1, 40.2, 46.5, 50.5, 64.3, 84.6, 122.4, 127.5, 128.2, 128.4, 131.5, 136.3, 174.8; IR (neat) 2929, 1664, 1456 cm^{-1}; exact mass, m/z 415.2535 (calcd for $C_{24}H_{37}NO_3Si$ m/z 415.2542).



3-(2, 6, 6-Trimethyl-1-cyclohexyl)-2*E*-propenyl *N*-benzyl-propenoylhydroxamate (1g)

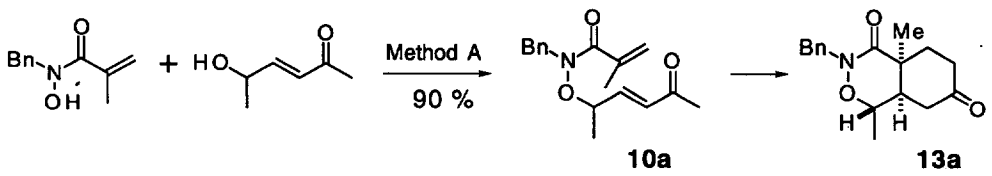
^{1}H NMR (500 MHz) δ 0.95 (s, 3H), 0.97 (s, 3H), 1.32 (d, 3H, *J* = 6.4 Hz), 1.40–1.46 (m, 2H), 1.55–1.62 (m, 2H), 1.63 (s, 3H), 1.93–2.00 (m, 2H), 4.40–4.48 (m, 1H), 4.82, 4.97 (ABq, 2H, *J* = 15.3 Hz), 5.40 (dd, 1H, *J* = 8.5, 15.9 Hz), 5.73 (dd, 1H, *J* = 1.8, 10.4 Hz), 5.98 (d, 1H, 15.9 Hz), 6.42 (dd, 1H, *J* = 1.8, 17.1 Hz), 6.80 (dd, 1H, 10.4, 17.1 Hz), 7.25–7.37 (m, 5H); ^{13}C NMR (50 MHz) δ 19.0, 19.7, 21.3, 28.5, 28.7, 32.6, 33.9, 39.3, 50.6, 82.1, 126.8, 127.4, 128.4 (2C), 128.8, 129.8, 132.0, 133.1, 136.2, 136.5, 167.1; IR (neat) 2930, 1658, 1460 cm^{-1}.

Cycloadduct (2g)

^{1}H NMR (500 MHz) δ 1.03 (s, 3H), 1.10 (s, 3H), 1.24 (s, 3H), 1.24 (d, 3H, *J* = 6.7 Hz), 1.42 (dd, 1H, *J* = 12.8, 13.4 Hz), 1.45–1.52 (m, 3H), 1.56–1.62 (m, 1H), 1.74–1.86 (m, 2H), 1.95 (dd, 1H, *J* = 3.7, 12.8 Hz), 2.38–2.44 (m, 1H), 2.86 (ddd, 1H, *J* = 3.7, 7.3, 13.4 Hz), 3.66–3.72 (m, 1H), 4.65 and 5.03 (ABq, 2H, *J* = 15.3 Hz), 5.22 (d, 1H, *J* = 3.7 Hz), 7.25–7.35 (m, 5H); ^{13}C NMR (50 MHz) δ 16.8, 18.4, 27.0, 29.7, 32.0, 34.8, 35.3, 35.6, 41.0, 41.4, 41.6, 44.1, 50.3, 77.8, 115.3, 127.4, 128.2, 128.4, 136.4, 154.1, 170.2; IR (neat) 2930, 1667, 1448 cm^{-1}; exact mass, m/z 339.2187 (calcd for $C_{22}H_{29}NO_2$ m/z 339.2198).

General procedure for the synthesis of 13

To a solution of **10** (0.5 mmol) and Et_3N (3 equiv) in THF (9 mL) was added TBSOTf (1.2 equiv) at room temperature. The mixture was stirred for 10 min. The reaction was quenched by the addition of water and extracted with AcOEt. The combined organic layers were dried with Na_2SO_4 and evaporated to give a crude oil, which was purified by CC to give **11** as a colorless oil. A solution of **11** (0.5 mmol) in toluene (10 mL) was warmed up to 90 °C and stirred at this temperature for 12 h. The mixture was evaporated to give **12** as a crude oil, which was dissolved in THF (5 mL). To the solution was added 2N HCl (2 mL) and the resulting mixture was stirred for 1 h at room temperature. The mixture was diluted with water and extracted with AcOEt. The combined organic layers were dried over Na_2SO_4 and evaporated to give a crude oil, which was purified by CC to give **13** as a colorless oil.

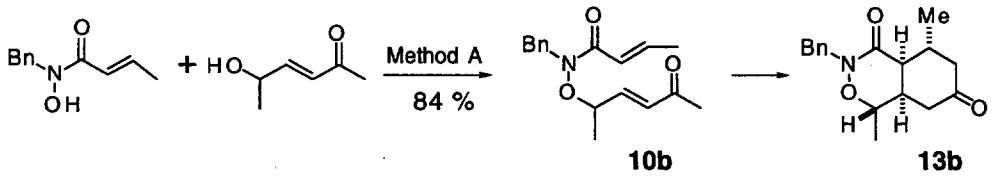


1-Methyl-4-oxo-(2*E*)-pentenyl *N*-benzyl-(2-methylpropenoyl)hydroxamate (10a).

^{1}H NMR (500 MHz) δ 1.26 (d, 3H, J = 6.4 Hz), 1.93 (s, 3H), 2.18 (s, 3H), 4.40–4.50 (m, 1H), 4.72, 4.80 (ABq, 2H, J = 15.6 Hz), 5.32 (s, 2H), 5.97 (d, 1H, J = 15.8 Hz), 6.52 (dd, 1H, J = 7.9, 15.8 Hz), 7.25–7.35 (m, 5H); ^{13}C NMR (75 MHz) δ 18.9, 19.8, 27.1, 53.6, 80.0, 118.5, 127.8, 128.1, 128.6, 131.8, 136.0, 140.1, 144.8, 172.4, 197.9; IR (neat) 1681, 1662, 1360 cm^{-1}.

Cycloadduct (13a)

^{1}H NMR (300 MHz) δ 1.18 (d, 3H, J = 6.3 Hz), 1.46 (s, 3H), 1.70–1.82 (m, 1H), 2.04–2.60 (m, 6H), 3.20 –3.52 (m, 1H), 4.60 and 4.95 (ABq, 2H, J = 15.1 Hz), 7.25–7.40 (m, 5H); ^{13}C NMR (75 MHz) δ 19.2, 26.0, 31.7, 36.5, 40.6, 42.2, 49.1, 50.3, 82.6, 127.8, 128.5, 128.6, 135.9, 173.1, 210.7; IR (neat) 2940, 1670, 1450 cm^{-1}; Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37. Found: C, 71.25; H, 7.52.

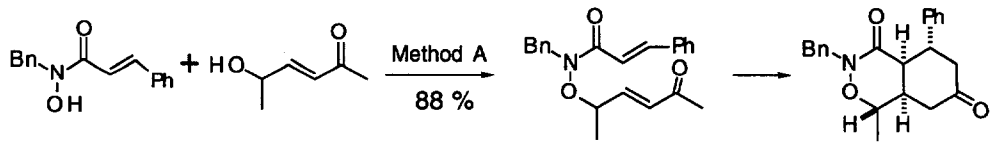


1-Methyl-4-oxo-(2*E*)-pentenyl *N*-benzyl-[(2*E*)-butenoyl]hydroxamate (10b).

^{1}H NMR (300 MHz) δ 1.36 (d, 3H, J = 6.5 Hz), 1.92 (dd, 3H, J = 1.6, 6.9 Hz), 2.20 (s, 3H), 4.42–4.55 (m, 1H), 4.75 and 4.89 (ABq, 2H, J = 15.4 Hz), 6.00 (d, 1H, J = 16.1 Hz), 6.44 (dd, 1H, J = 1.4, 15.1 Hz), 6.60 (dd, 1H, J = 7.1, 16.1 Hz), 7.04 (dq, 1H, J = 6.9, 15.1 Hz), 7.22–7.38 (m, 5H); ^{13}C NMR (75 MHz) δ 18.4, 18.8, 27.3, 51.6, 79.7, 120.6, 127.6, 128.2, 128.4, 131.9, 136.4, 143.8, 144.0, 168.1, 197.7; IR (neat) 1680, 1664, 1350 cm^{-1}.

Cycloadduct (13b)

^{1}H NMR (300 MHz) δ 1.05 (d, 3H, J = 6.9 Hz), 1.19 (d, 3H, J = 6.3 Hz), 2.02–2.22 (m, 3H), 2.41–2.98 (m, 4H), 3.42–3.55 (m, 1H), 4.62 and 4.93 (ABq, 2H, J = 14.9 Hz), 7.23–7.40 (m, 5H); ^{13}C NMR (75 MHz) δ 19.0, 19.9, 28.8, 42.1, 42.9, 43.8, 45.1, 49.8, 82.3, 127.9, 128.6 (2C), 135.8, 171.5, 209.6; IR (neat) 1668, 1640, 1448 cm^{-1}; exact mass, m/z 287.1532 (calcd for $C_{17}H_{21}NO_3$ m/z 287.1521).

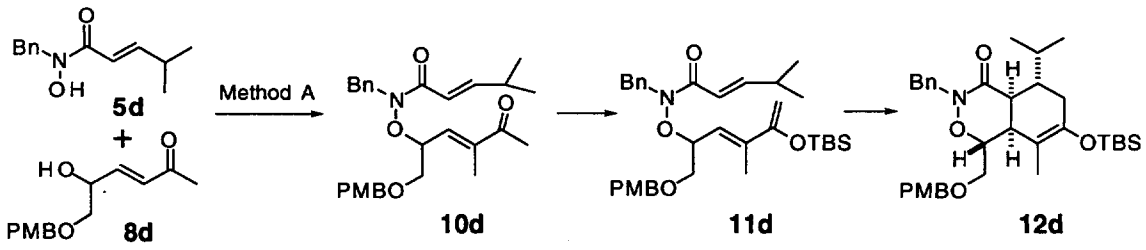


10c 13c

1-Methyl-4-oxo-(2*E*)-pentenyl *N*-benzyl-3-phenyl-[(2*E*)-propenoyl]hydroxamate (10c). ^{1}H NMR (300 MHz) δ 1.40 (d, 3H, *J* = 6.3 Hz), 2.16 (s, 3H), 4.50–4.60 (m, 1H), 4.83 and 4.97 (ABq, 2H, *J* = 15.6 Hz), 6.06 (d, 1H, *J* = 15.9 Hz), 6.52 (dd, 1H, *J* = 7.1, 15.9 Hz), 7.08 (d, 1H, *J* = 15.9 Hz), 7.20–7.60 (m, 10H), 7.78 (d, 1H, *J* = 15.9 Hz); ^{13}C NMR (75 MHz) δ 18.9, 27.3, 51.8, 80.1, 116.1, 127.7, 128.0, 128.3, 128.6, 128.9, 130.1, 132.1, 134.9, 136.3, 143.6, 144.1, 168.2, 197.7; IR (neat) 3030, 1680, 1350 cm^{-1}.

Cycloadduct (13c)

^{1}H NMR (300 MHz) δ 1.09 (d, 3H, *J* = 6.3 Hz), 2.12–2.43 (m, 3H), 2.70 (dd, 1H, *J* = 5.2, 15.6 Hz), 3.04 (dd, 1H, *J* = 6.3, 15.6 Hz), 3.04–3.15 (m, 1H), 3.42–3.54 (m, 1H), 4.05–4.15 (m, 1H), 4.56 and 4.99 (ABq, 2H, *J* = 15.1 Hz), 7.18–7.40 (m, 10H); ^{13}C NMR (75 MHz) δ 18.9, 38.3, 41.3, 42.5, 43.7, 44.2, 49.9, 82.6, 126.8, 127.4, 128.0, 128.6, 128.71, 128.73, 135.7, 143.2, 171.3, 209.6; IR (neat) 3030, 1667, 1640, 1448 cm^{-1}; exact mass, m/z 349.1665 (calcd for $C_{22}H_{23}NO_3$ m/z 349.1678).



5d 8d 10d 11d 12d

1-(4-Methoxybenzyloxy)methyl-3-methyl-4-oxo-(2*E*)-pentenyl *N*-benzyl-[4-methyl-(2*E*)-pentenoyl]hydroxamate (10d)

To a solution of 6-*O*-(4-methoxybenzyl)-3-methyl-5,6-dihydroxy-(*3E*)-hexen-2-one (**8d**) (371 mg, 1.40 mmol), *N*-benzyl-*N*-hydroxy-4-methyl-(*2E*)-pentenamide (**5d**) (767 mg, 2.5 equiv) and Ph_3P (1.28 g, 3.5 equiv) in THF (40 mL) was added DEAD (0.77 mL, 3.5 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. It was filtered through a celite pad, and the filter cake was thoroughly rinsed with hexane/AcOEt, 3:1. The combined organic filtrates were evaporated to give a crude oil, which was purified

by CC to give **10d** (308 mg, 47 %): ^{1}H NMR (300 MHz) δ 0.98–1.06 (m, 6H), 1.60 (d, 3H, *J* = 1.4 Hz), 2.21 (s, 3H), 2.39 (m, 1H), 3.49 (dd, 1H, *J* = 11.3, 3.6 Hz), 3.55 (dd, 1H, *J* = 11.26, 6.0 Hz), 3.78 (s, 3H), 4.42–4.47 (m, 2H), 4.83–4.87 (m, 3H), 6.46 (dq, 1H, *J* = 8.8, 1.4 Hz), 6.62 (d, 1H, *J* = 15.4 Hz), 6.88 (dt, 2H, *J* (doublet) = 8.5 Hz), 7.00 (dd, 1H, *J* = 15.7, 6.6 Hz), 7.25–7.38 (m, 7H); ^{13}C NMR (300 MHz) δ 11.64, 21.41, 25.55, 31.23, 51.63, 55.22, 69.39, 73.11, 81.45, 113.74, 116.51, 127.53, 128.21, 128.45, 129.29, 129.37, 135.85, 136.53, 140.70, 155.06, 159.29, 168.70, 198.94; IR (neat) 1680, 1661, 1362 cm^{-1}.

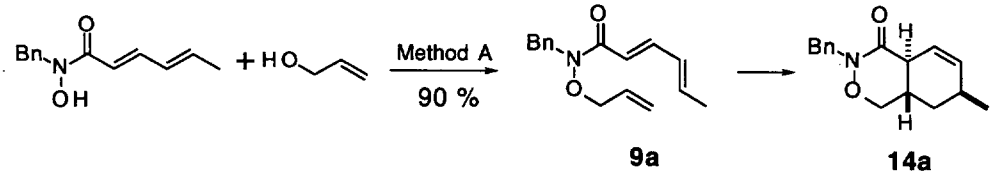
4-(*tert*-Butyldimethylsiloxy)-1-(4-methoxybenzyloxy)methyl-3-methyl-(2*E*,4)-pentadienyl *N*-benzyl-[4-methyl-(2*E*)-pentenoyl]hydroxamate (11d)

To a solution of **10d** (308 mg, 0.66 mmol) and Et_3N (0.55 mL, 6.0 equiv) in THF (9 mL) was added TBSOTf at room temperature. The mixture was stirred for 10 min. The reaction was quenched by the addition of water and extracted with AcOEt. The combined organic layer was dried with Na_2SO_4 and evaporated to give a crude oil, which was purified by CC to give **11d** as a colorless oil (229 mg, 59 %): ^{1}H NMR (300 MHz) δ 0.15 (s, 3H), 0.18 (s, 3H), 0.96 (s, 9H), 1.01 (d, 6H, *J* = 6.6 Hz), 1.70 (s, 3H), 2.30–2.40 (m, 1H), 3.47 (dd, 1H, *J* = 11.0, 3.0 Hz), 3.58 (dd, 1H, *J* = 11.0, 7.2 Hz), 3.80 (s, 3H), 4.35–4.52 (m, 4H), 4.72 and 5.02 (ABq, 2H, *J* = 15.4 Hz), 4.86 (m, 1H), 6.02–6.10 (m, 1H), 6.66 (d, 1H, *J* = 9.9 Hz), 6.88 (dt, 2H, *J* (doublet) = 8.5 Hz), 6.95 (dd, 1H, *J* = 6.9, 15.4 Hz), 7.20–7.33 (m, 7H); ^{13}C NMR (300 MHz) d –4.79, –4.61, 13.69, 18.21, 21.43, 21.46, 25.78, 31.12, 51.04, 55.16, 70.73,73.04, 81.81, 93.40, 113.63, 116.87, 121.86, 127.20, 128.23, 128.45, 129.25, 129.81, 1 36.73, 137.15, 154.10, 156.07, 159.13, 168.46; IR (neat) 2950, 1665, 1640 cm^{-1}.

Cycloadduct (12d)

A solution of **11d** (229 mg, 0.39 mmol) in toluene (7 mL) was stirred at 100 °C for 12 h. The mixture was evaporated to give a crude oil, which was purified by CC to give **12d** as a colorless oil (191 mg, 85 %): ^{1}H NMR (300 MHz) δ 0.11 (d, 6H, *J* = 0.9 Hz), 0.94 (m, 15H), 1.46 (s, 3H), 1.60–2.00 (m, 2H), 2.19–2.29 (m, 2H), 2.35 (t, 1H, *J* = 5.5 Hz), 2.65 (dd, 1H, *J* = 6.3, 1.4 Hz), 3.41 (m, 2H), 3.80 (s, 3H), 4.00 (ddd, 1H, *J* = 15.1, 8.8, 4.9 Hz), 4.30 (s, 2H), 4.40–5.00 (m, 2H), 6.88 (dt, 2H, *J* (doublet) = 8.5 Hz), 7.20–7.33 (m, 7H); ^{13}C NMR (300 MHz) δ –3.89, –3.85, 14.25, 18.15, 20.62, 25.78, 28.45, 29.32, 37.65, 40.42, 42.51, 50.05, 55.20, 70.40, 72.58, 83.86, 109.59, 113.71, 127.54, 128.37, 128.61, 129.24, 129.38, 129.68, 1

36.20, 144.42, 159.19, 172.33; IR (neat) 2950, 1670, 1640 cm^{-1}; exact mass, m/z 579.3375 (calcd for $C_{34}H_{49}NO_5Si$ m/z 579.3380).



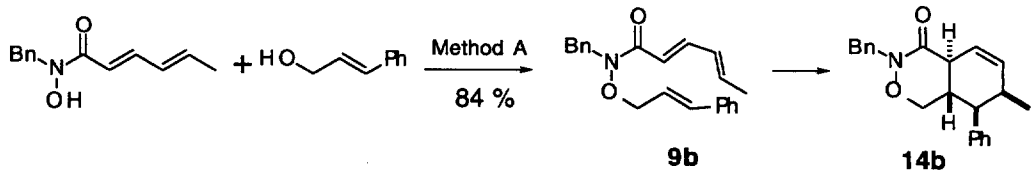
9a **14a**

2-Propenyl *N*-benzyl-[(2*E*,4*E*)-hexadienoyl]hydroxamate (9a)

^1H NMR (300 MHz) δ 1.84 (d, 3H, *J* = 6.3 Hz), 4.24–4.30 (m, 2H), 4.86 (s, 2H), 5.25–5.35 (m, 2H), 5.88 (ddt, 1H, *J* = 6.3, 10.4, 16.5 Hz), 6.13–6.32 (m, 2H), 6.41 (d, 1H, *J* = 15.7 Hz), 7.28–7.35 (m, 6H); ^{13}C NMR (75 MHz) δ 18.4, 50.1, 76.1, 116.8, 120.2, 127.3, 128.2, 128.3, 130.1, 131.1, 136.4, 138.5, 144.1, 167.6; IR (neat) 1789, 1654, 1244 cm^{-1}.

Cycloadduct (14a)

^1H NMR (300 MHz) δ 1.00 (d, 3H, *J* = 7.2 Hz), 1.50–1.59 (m, 1H), 1.73 (dt, 1H, *J* = 6.3, 12.9 Hz), 1.98–2.15 (m, 1H), 2.32–2.45 (m, 1H), 2.95–3.05 (m, 1H), 3.55 (dd, 1H, *J* = 8.5, 10.2 Hz), 4.15 (dd, 1H, *J* = 8.8, 10.2 Hz), 4.57 and 4.93 (ABq, 2H, *J* = 15.4 Hz), 5.72–5.80 (m, 1H), 6.15 (dt, 1H, *J* = 1.9, 10.2 Hz), 7.25–7.37 (m, 5H); ^{13}C NMR (75 MHz) δ 21.0, 28.9, 32.2, 33.3, 40.6, 49.5, 74.4, 121.2, 127.6, 128.2, 128.5, 134.2, 136.3, 173.4; IR (neat) 1676, 1430, 1240 cm^{-1}; exact mass, m/z 257.14127 (calcd for $C_{16}H_{19}NO_2$ m/z 257.1416).



9b **14b**

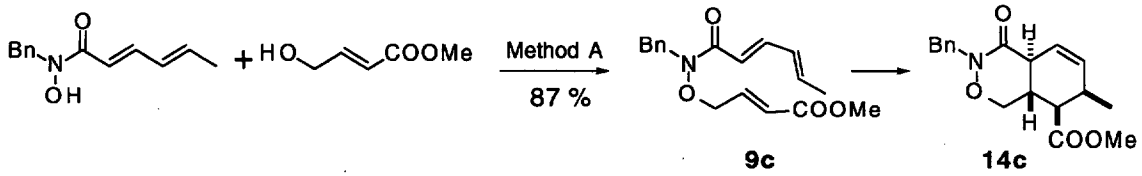
3-Phenyl-(2*E*)-propenyl *N*-benzyl-[(2*E*,4*E*)-hexadienoyl]hydroxamate (9b)

^1H NMR (300 MHz) δ 1.87 (d, 3H, *J* = 6.0 Hz), 4.43 (d, 1H, *J* = 6.3 Hz), 4.92 (s, 2H), 6.08–6.33 (m, 3H), 6.48 (d, 1H, *J* = 15.1 Hz), 6.57d, 1H, *J* = 15.9 Hz), 7.23–7.42 (m, 11H); ^{13}C NMR (75 MHz) δ 18.4, 50.3, 75.9, 116.9, 121.8, 126.4, 127.3, 128.0, 128.2, 128.3, 128.4, 130.1, 135.5, 137.7, 136.5, 138.5, 144.1, 167.7; IR (neat) 3030, 1790, 1631 cm^{-1}.

Cycloadduct (14b)

^1H NMR (300 MHz) δ 0.72 (d, 3H, *J* = 7.2 Hz), 2.42–2.65 (m, 2H), 3.23 (dd, 1H, *J* = 5.5, 11.8 Hz), 3.30–3.40 (m, 1H), 3.48 (dd, 1H, *J* = 8.5, 10.3 Hz), 4.17 (dd, 1H, *J* = 8.8, 10.7 Hz),

4.68 and 4.97 (ABq, 2H, J = 15.1 Hz), 5.92–6.00 (m, 1H), 6.24 (dt, 1H, J = 1.9, 10.0 Hz), 7.02–7.30 (m, 10 H); ^{13}C NMR (75 MHz) δ 16.5, 34.3, 36.1, 41.9, 49.3, 49.6, 73.6, 120.6, 126.6, 127.6, 127.7, 128.2, 128.4, 128.5, 129.5, 134.8, 140.5, 173.6; IR (neat) 3030, 1675, 1430 cm^{-1}; exact mass, m/z 333.1731 (calcd for $C_{22}H_{23}NO_2$ m/z 333.1729).

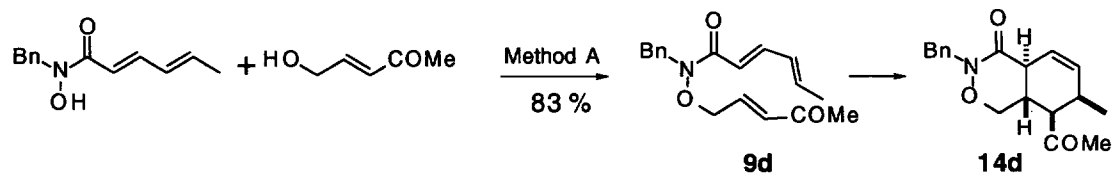


3-Methoxycarbonyl-(2*E*)-propenyl *N*-benzyl-[(2*E*,4*E*)-hexadienoyl]hydroxamate (9c)

^{1}H NMR (500 MHz) δ 1.85 (d, 3H, J = 6.1 Hz), 3.75 (s, 3H), 4.39 (dd, 2H, J = 1.8, 5.0 Hz), 4.86 (s, 2H), 6.00 (d, 1H, J = 15.9 Hz), 6.16 (dq, 1H, J = 13.4, 6.1 Hz), 6.24 (dd, 1H, J = 15.3, 15.9 Hz), 6.32 (d, 1H, J = 5.3 Hz), 6.85 (dt, 1H, J = 15.9, 5.3 Hz), 7.25–7.30 (m, 1H), 7.30–7.33 (m, 5H), 7.37 (dd, 1H); ^{13}C NMR (50 MHz) δ 18.5, 50.6, 51.6, 73.7, 116.2, 122.9, 127.6, 128.4, 128.5, 130.1, 136.2, 139.2, 140.1, 144.9, 165.9, 167.9; IR (neat) 2951, 1728, 1659 cm^{-1}.

Cycloadduct (14c)

^{1}H NMR (500 MHz) δ 0.86 (d, 3H, J = 6.8 Hz), 2.25–2.35 (m, 1H), 2.66–2.75 (m, 1H), 2.89 (dd, 1H, J = 6.3, 11.7 Hz), 3.10–3.16 (m, 1H), 3.59 (dd, 1H, J = 8.3, 10.8 Hz), 3.67 (s, 1H), 4.37 (dd, 1H, J = 8.8, 10.8 Hz), 4.60 and 4.90 (ABq, 2H, J = 15.1 Hz), 5.77–5.81 (m, 1H), 6.12–6.27 (m, 1H), 7.33–7.36 (m, 5H, ArH); ^{13}C NMR (50 MHz) δ 16.6, 32.1, 33.0, 40.2, 49.1, 49.5, 51.6, 73.9, 121.2, 127.7, 128.2, 128.5, 132.9, 135.9, 172.9, 173.2; IR (neat) 3018, 1732, 1674 cm^{-1}; Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71. Found: C, 68.33; H, 6.92.



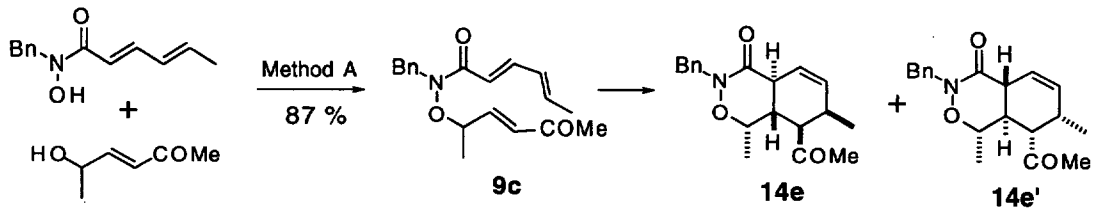
4-Oxo-(2*E*)-pentenyl *N*-benzyl-[(2*E*,4*E*)-hexadienoyl]hydroxamate (9d)

^{1}H NMR (500 MHz) δ 1.84 (d, 3H, J = 6.2 Hz), 2.23 (s, 3H), 4.41 (dd, 2H, J = 1.8, 5.2 Hz), 4.86 (s, 2H), 6.13–6.27 (m, 2H), 6.32 (d, 1H, J = 15.3 Hz), 6.63 (dt, 1H, J = 16.2, 5.2 Hz), 7.25–7.30 (m, 1H), 7.30–7.34 (m, 5H), 7.38 (dd, J = 10.7, 15.0 Hz); ^{13}C NMR (50 MHz) δ

18.5, 27.1, 50.5, 73.8, 116.2, 127.5, 128.2, 128.4, 129.9, 131.8, 136.1, 138.3, 139.2, 144.8, 167.8, 197.3; IR (neat) 3030, 1678, 1660 cm^{-1}.

Cycloadduct (14d)

^1H NMR (500 MHz) δ 0.80 (d, 3H, *J* = 7.0 Hz), 2.14 (s, 3H), 2.27 (ddt, 1H, *J* (d) = 11.3, 11.6 Hz, *J* (t) = 8.4 Hz), 2.75–2.83 (m, 1H), 3.00 (dd, 1H, *J* = 5.8, 11.3 Hz), 3.09 (ddd, 1H, *J* = 1.8, 4.3, 11.6 Hz), 3.43 (dd, 1H, *J* = 7.9, 11.0 Hz), 4.40 (dd, 1H, *J* = 8.9, 11.0 Hz), 4.61 and 4.86 (ABq, 2H, *J* = 15.3 Hz), 5.78–5.83 (m, 1H), 6.15 (ddd, 1H, *J* = 1.8, 4.0, 10.1 Hz), 7.26–7.38 (m, 5H); ^{13}C NMR (50 MHz) δ 16.3, 28.6, 31.6, 32.6, 40.1, 49.5, 57.4, 73.9, 121.7, 127.7, 128.2, 128.5, 132.8, 135.9, 173.0, 208.7; IR (neat) 2968, 1709, 1674 cm^{-1}; exact mass, m/z 299.1509 (calcd for $C_{18}H_{21}NO_3$ m/z 299.1521).



1-Methyl-4-oxo-(2*E*)-pentenyl *N*-benzyl-[(2*E*,4*E*)-hexadienyl]hydroxamate (9e)

^1H-NMR (500 MHz); δ 1.26 (d, 3H, *J* = 6.4 Hz), 1.85 (d, 3H, *J* = 6.3 Hz), 2.24 (s, 3H), 4.40–4.52 (m, 1H), 4.85 (s, 2H), 6.15–6.28 (m, 2H), 6.32 (d, 1H, *J* = 15.3 Hz), 6.63 (dt, 1H, *J* = 16.2 Hz, *J* = 5.2 Hz), 7.25–7.30 (m, 1H), 7.30–7.34 (m, 5H), 7.38 (dd, *J* = 10.7, 15.0 Hz); ^{13}C NMR (50 MHz) δ 18.4, 18.9, 27.1, 50.3, 75.2, 116.3, 127.4, 128.1, 128.6, 129.8, 131.7, 136.2, 138.2, 139.1, 144.8, 167.7, 198.1; IR (neat) 3030, 1678, 1660 cm^{-1}.

Cycloadduct 14 e (major diastereomer)

Cycloadduct **14e** and **14e'** were obtained as a separable mixture of diastereomers. The stereochemistries of these cycloadducts were determined by careful analysis of ^1HNMR spectra (*J* value, NOE) of the mixture. ^1H NMR (500 MHz); δ 0.80 (d, 3H, *J* = 7.0 Hz), 1.38 (d, 3H, *J* = 6.4 Hz), 1.85 (ddd, 1H, *J* = 6.1, 11.6, 11.6Hz), 2.15 (s, 3H), 2.72–2.78 (m, 1H), 3.07 (dd, 1H, *J* =2.1, 11.6Hz), 3.13 (dd, 1H, *J* = 5.8, 11.6 Hz), 3.85 (dq, 1H, *J* = 6.1, 6.1 Hz), 4.52 and 4.98 (ABq, 2H, *J* = 15.0 Hz), 5.62–5.78 (m, 1H), 6.15 (d, 1H, *J* = 9.8 Hz), 7.26–7.38 (m, 5H); IR (neat) 2971, 1710, 1675 cm^{-1}; exact mass, m/z 313.1662 (calcd for $C_{19}H_{23}NO_3$ m/z 313.1678).

Cyclic hemiacetal (16)

To a suspension of $LiAlH_4$ (11 mg, 1.5 equiv) in THF (3 mL) was added a solution of **2b** (51 mg, 0.19 mmol) in THF (2 mL) at 0 °C. The mixture was stirred at 0 °C for 5 h. The reaction was quenched by the addition of water and the mixture was extracted with AcOEt. The combined organic layers were dried with Na_2SO_4 and evaporated to give **15** as a crude oil. To a suspension of $Cu(OAc)_2$ (4.5 mg, 0.02 mmol) in AcOH (1 mL) was added zinc dust (67 mg, 5 equiv) at room temperature. The mixture was stirred at room temperature for 15 min. To this was added a solution of the crude **15** in AcOH–water (4:1 w/w) mixed solvent (2 mL). The mixture was stirred at 70 °C for 5.5 h. The reaction was quenched by the addition of saturated aqueous solution of $NaHCO_3$ and extracted with AcOEt. The combined organic layers were dried with Na_2SO_4 and evaporated to give an oil, which was purified by CC to give **16** as a colorless oil (24 mg, 77 %): Data for major diastereomer: ^{1}H NMR (300 MHz) δ 1.00 (d, 3H, J = 7.2 Hz), 1.06 (s, 3H), 1.34–1.50 (m, 1H), 2.18–2.73 (m, 3H), 3.48–3.58 (m, 1H), 4.28 (dd, 1H, J = 8.0, 9.3 Hz), 4.92 (b, 1H), 5.50–5.64 (m, 2H); ^{13}C NMR (75 MHz) δ 17.7, 21.5, 27.0, 37.5, 41.7, 44.7, 73.6, 105.1, 124.3, 133.2; IR (neat) 3450, 1260, 1150 cm^{-1}.

Theoretical calculations

The optimized structure of **1a** was investigated by the Hartree-Fock level calculation using Gaussian98 program package. Two basis sets used were 3-21G and 6-31G(d). Two local minima were obtained, and they corresponded to the conformer C (anti-form) and the conformer A (syn-form). The anti-form was found to be more stable with either basis set. The energy difference between conformers was calculated to be 6.5 kcal/mol with the 3-21G, whereas it reduced to 4.4 kcal/mol with the 6-31G(d).