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Regiospecific synthesis of a bridgehead-functionalized bicyclo[2.2.2]octenone

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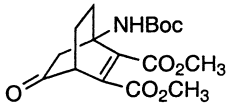
Abstract—Three independent strategies are tested toward the synthesis of the protected 1-aminobicyclo[2.2.2]octene ketodiester **1**. One of these three is found to be completely regioselective. It proceeds by Diels–Alder addition of dimethyl acetylenedicarboxylate to the silyl enol ether of 3-benzyloxycarbonyl-2-cyclohexenone, followed by a chemoselective Curtius rearrangement.

Bicyclo[2.2.2]octanes bearing a free or protected NH_2 group at the bridgehead have served as scaffolds for antiviral agents,[1,2] as inhibitors of phenylethanolamine *N*-methyl transferase[3] and as ligands for the phencyclidine[4] and dopamine[5] receptors. In contrast, the literature on analogous bicyclo[2.2.2]octenes is sparse,[6] and highly functionalized ring derivatives appear to be unknown. We now report a comparison of three synthetic strategies directed toward the protected amino ketone diester **1** in this series.



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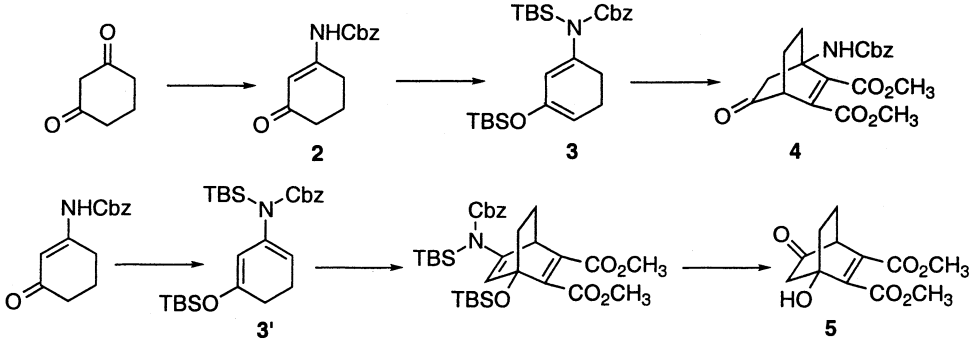
Our initial approach to **1** attempted to parallel earlier work by Wolinsky and Login toward bridgehead carbinols in this system.[7] Starting from 1,3-cyclohexanedione, we prepared the vinylogous urea **2**.[8] The latter was converted to an *O*,*N*-bis-silyl derivative, formulated as **3**. This was subjected to Diels–Alder reaction with dimethyl acetylenedicarboxylate to yield an adduct, expected to yield on mild acid hydrolysis the bridgehead carbamate **4**.

To our surprise, hydrolysis of the initial Diels–Alder adduct gave a product ketone devoid of nitrogen, namely the bridgehead hydroxy ketone **5** previously prepared by Wolinsky.[7] It thus became clear that the diene initially assigned structure **3** was in fact the regioisomer **3′**, and that the isolation of **5** as the final product had proceeded by the parallel Diels–Alder sequence picture below. Thus, enolization of **2** had followed the pathway noted by Bryson and Gammill, involving enolization at C(4) of the cyclohexenone system.[9]



Keywords: Diels–Alder reaction; enols and derivatives; Curtius rearrangement; bicyclooctenones; regiospecificity.
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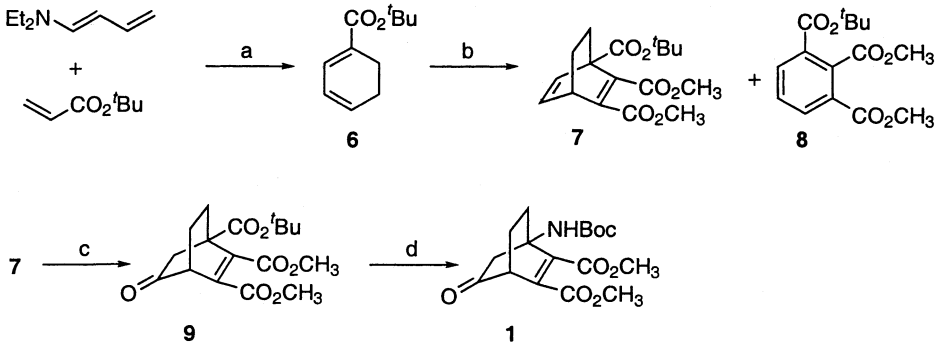
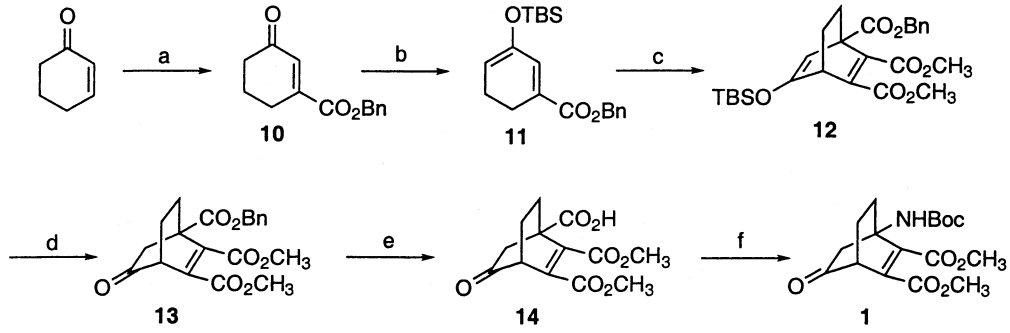


Scheme 1. *Reagents and conditions*: (a) i. 40°C, 2 days, ii. CH_3I, CH_2Cl_2, iii. DBU, CH_2Cl_2, 67%; (b) dimethyl acetylenedicarboxylate, *N*,*N*-dimethylaniline, 80°C, 69%; (c) i. catecholborane, 2 mol% $Rh(PPh_3)_3Cl$, THF, then H_2O_2, Buffer pH 7.0, ii. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 ~ −60°C, 55%; (d) i. 30% CF_3CO_2H, CH_2Cl_2, ii. $(COCl)_2$, DMF, CH_2Cl_2, iii. NaN_3, acetone/H_2O (3:1), iv. *t*-butanol, reflux, 63%.



Scheme 2. *Reagents and conditions*: (a) see Ref. 14; (b) TBSOTf, Et_3N, CH_2Cl_2, 0°C; (c) dimethyl acetylenedicarboxylate, 80°C, 66% from **10**; (d) 1 M TBAF, THF, 91%; (e) Raney-Ni, ethanol, (f) i. $(COCl)_2$, DMF, CH_2Cl_2, ii. NaN_3, acetone/H_2O (3:1), iii. *t*-butanol, reflux, 55% from **13**.

To overcome this problem, we sought to introduce the bridgehead nitrogen by Curtius rearrangement.[6] Diels–Alder addition of 1-(*N*,*N*-dimethylamino)-1,3-butadiene[10] to *t*-butyl acrylate gave adducts which upon Hoffman elimination gave in 67% yield the diene ester **6**.[11] Reaction of this ester with excess dimethyl acetylenedicarboxylate in the presence of 5 mol% Me_2NPh gave 69% of the bicyclo[2.2.2]octadiene triester **7**, accompanied by ca. 10% of the *retro*-Diels–Alder product **8**.[12] Hydroboration of diene **7** with B_2H_6 gave no selectivity. However, reaction with catecholborane and $Rh(PPh_3)_3Cl$ as catalyst[13] proceeded with moderate regioselectivity to yield, after neutral H_2O_2 workup and Swern oxidation, a 55% yield of the ketone **9**. Trifluoroacetic acid cleavage of the *t*-butyl ester, then successive conversion of the carboxyl group to acid chloride and then acyl azide, followed by overnight reflux in *t*-BuOH gave the desired target **1** in 63% yield from **9** (Scheme 1).[16]

Finally, a completely regioselective third approach to the protected aminoketone **1** was achieved starting from 2-cyclohexenone. Conversion of the latter to the 3-benzyloxycarbonyl derivative **10** by a known procedure[14] was followed by treatment of **10** with TBSOTf and Et_3N to give the diene ester **11**.[15] Diels–Alder reaction of **11** with dimethyl acetylenedicarboxylate gave adduct **12** which on hydrolysis produced ketone **13** in 60% overall yield from **11**. Hydrogenation of **13** over Raney-Ni chemoselectively produced the bicyclooctene acid **14**. Curtius rearrangement by the sequence described above gave the protected aminoketone **1** in 55% yield from **13**. The last route comprises an efficient sequence to this highly functionalized bicyclo[2.2.2]octene system (Scheme 2).[16]

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16. Selected spectroscopic data; **7**: colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.52 (s, 9H), 1.55–1.70 (m, 3H), 1.81–1.88 (m, 1H), 3.76 (s, 3H), 3.86 (s, 3H), 4.18–4.23 (m, 1H), 6.47 (dd, $J=6.1$, 7.4 Hz, 1H), 6.57 (dd, $J=1.6$, 7.4 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.9, 27.8 (3×C), 30.2, 37.9, 51.97, 52.00, 55.3, 81.8, 133.1, 134.0, 137.8, 146.0, 164.1, 166.7, 170.7 ppm; anal. calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.22; H, 6.84%; **9**: mp 144–145°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.52 (s, 9H), 1.80–1.90 (m, 1H), 1.95–2.05 (m, 3H), 2.38 (d, $J=18.7$ Hz, 1H), 2.48 (dd, $J=2.5$, 18.7 Hz, 1H), 3.79 (s, 3H), 3.79–3.82 (m, 1H), 3.84 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.1, 27.6 (3×C), 29.0, 41.4, 48.7, 51.5, 52.2, 52.4, 82.5, 130.8, 146.6, 163.1, 166.0, 170.0, 206.6 ppm; anal. calcd for $C_{17}H_{22}O_7$: C, 60.35; H, 6.55. Found: C, 60.14; H, 6.46%; **1**: mp 152–153°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.34 (s, 9H), 1.67–1.73 (m, 1H), 1.86–1.96 (m, 3H), 2.26 (d, $J=18.4$ Hz, 1H), 2.92 (dd, $J=2.8$, 18.4 Hz, 1H), 3.61–3.65 (m, 1H), 3.68 (s, 3H), 3.70 (s, 3H), 5.08 (brs. 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.6, 28.0 (3×C), 30.1, 43.5, 48.1, 52.2, 52.4, 57.5, 79.9, 130.0, 147.8, 154.4, 163.3, 165.4, 205.7 ppm; anal. calcd for $C_{17}H_{23}NO_7$: C, 57.78; H, 6.56; N, 3.96. Found: C, 57.88; H, 6.32; N, 3.91%.