



## An improved synthesis of diiodonoradamantane

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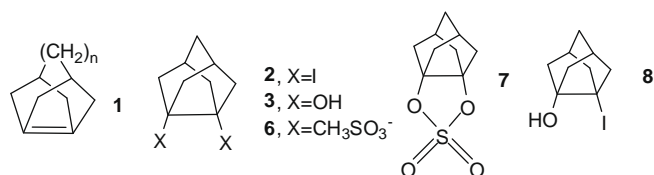
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### ABSTRACT

The synthesis of 3,7-diiodo-tricyclo[3.3.1.0<sup>3,7</sup>]nonane, the main precursor of noradamantene, by iodination of the corresponding diol via its dimesylate affords a threefold higher yield than the direct iodination of the diol. Neither the dimesylate nor the cyclic sulfate of the diol yields noradamantene upon reduction with sodium amalgam.

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Pyramidalized alkenes<sup>1</sup> have attracted a great deal of attention because of their interesting properties.<sup>2,3</sup> The homologous series of pyramidalized alkenes **1** has been studied systematically, and the first four members (**1**,  $n = 0-3$ ) have been generated. Herein we describe research directed towards improving the synthesis of noradamantene (**1**,  $n = 1$ ) with the aim of using this molecule as a building block for the synthesis of other polycyclic organic molecules.



Noradamantene can be generated conveniently and quantitatively by reduction of diiodide **2**.<sup>4</sup> The only known synthetic route to **2** is via iodination of diol **3**. Diol **3** can be prepared<sup>5</sup> from adamantane in 36% overall yield (route 1),<sup>6</sup> from adamantanone in 60% overall yield (route 2)<sup>7</sup> or via condensation of dimethyl 1,3-acetonedicarboxylate (**4**) with 1,1,3,3-tetramethoxypropane (**5**)<sup>8</sup> in 50% overall yield (route 3) (Scheme 1). The third route is slightly less efficient than the second route, but requires one less step and simpler reactions and is the route to **3** that we have followed.

The iodination of **3** to **2** requires harsh conditions [48 h at 110 °C in 95% phosphoric acid and an excess (six times the required stoichiometric amount) of NaI] with a reported yield of 40%.<sup>4</sup> Our efforts to produce **2** from **3** under similar conditions resulted in yields of 20% at best (Table 1).

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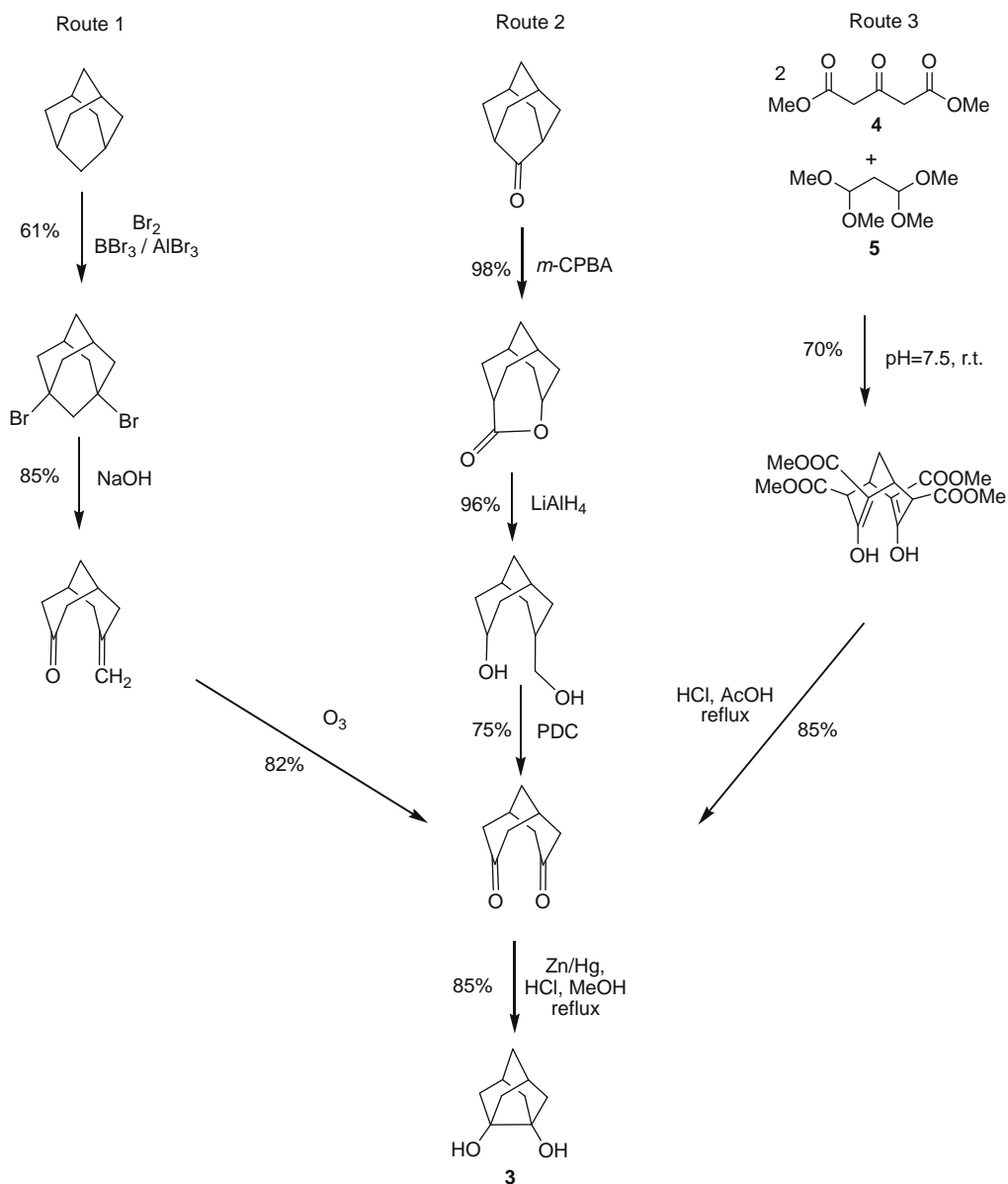
Alkenes **1**,  $n = 2, 3$  can be easily formed at room temperature by reduction of their corresponding dimesylates with Na/Hg.<sup>9</sup> Dimesylate **6** can be easily obtained from diol **3** following the known protocols, in almost quantitative yield.<sup>10-12</sup> However, **6** is not reduced by Na/Hg, neither at room temperature nor in refluxing THF. Attempts to form the ditosylate of diol **3** led to the quantitative formation of the monotosylate, presumably due to steric hindrance.

Iodination of dimesylate **6** was attempted under a variety of conditions (Table 2).<sup>13</sup> No reaction was observed when ionic liquids were used as solvents (Table 2, entries 1–5), even with I<sup>-</sup> as the counter ion. When methanesulfonic acid (entry 6) was used as the solvent, only a trace of diiodide (<5%) was observed, however, some diol **3** was recovered along with starting material **6**.

Concentrated phosphoric acid appears to be the best solvent for preparing **2** from **6**, in agreement with the previous reports on the preparation of **2** from **3**.<sup>4</sup> We used commercially available 99% phosphoric acid (mp 40 °C) for this reaction. No special precautions were taken to exclude atmospheric moisture from the reaction mixture. The nature of the iodinating agent (Table 2, entries 7, 13, and 14) does not appear to be important since NaI, KI, and CsI gave similar results. However, a large excess of NaI significantly increased the yield. The optimum excess appeared to be around a molar ratio of 60:1 (NaI:6) (Table 2, entry 18).

The reaction was monitored by gas chromatography. Dimesylate **6** was fully consumed within the first 4 h, forming diiodide **2** and a small amount of monoiodide **8**.<sup>14</sup> After an additional two hours, only **2** was detected. Reaction times greater than one day tended to lower the yield.

Diol **3** and dimesylate **6** react almost quantitatively (90% yield) with concentrated sulfuric acid to give the cyclic sulfate ester **7**.<sup>15</sup> Although cyclic sulfate esters are considered quite reactive and have found numerous synthetic applications recently, this was not the case with **7**.<sup>16</sup> Attempts to reduce **7** to noradamantene (**1**,  $n = 1$ ) with Na/Hg were not successful. Also, iodination of **7** was much slower than that of **6**, requiring more than four days



Scheme 1. Synthetic routes to diol 3.

and resulting in a yield of less than 15%. We attribute this relative lack of reactivity to the structure of **7**, which unlike other known cyclic sulfates, is formally derived from a bis-tertiary vicinal diol. In addition, the tricyclic cage is such that neither rear attack nor

the facile formation of a (pyramidal) tertiary carbocation is possible.

In conclusion, the best precursor for the generation of noradamantene under ambient conditions remains diiodide **2** which is

**Table 1**  
Synthesis of diiodide **2** from diol **3**

Entry	Diol <b>3</b> (mmol)	Solvent (%)	$\text{NaI}:\mathbf{3}^a$	$T^b$ ( $^\circ\text{C}$ )	$t$ (d)	% Yield of <b>2</b> <sup>c</sup>
1	1.9	$\text{H}_3\text{PO}_4$ (85)	15	120	7	10
2	1.3	$\text{H}_3\text{PO}_4$ (85)	15	120	2	13
3	0.4	$\text{H}_3\text{PO}_4$ (85)	15	140	3	8
4	0.6	$\text{H}_3\text{PO}_4$ (99)	15	150	2	15
5	6.5	$\text{H}_3\text{PO}_4$ (99)	15	150	4	20
6	0.6	$\text{H}_3\text{PO}_4$ (99)	50	130	1	18

<sup>a</sup> Molar ratio of  $\text{NaI}$  to **3**.

<sup>b</sup> External bath temperature.

<sup>c</sup> Yield of crude product.

**Table 2**  
Synthesis<sup>13</sup> of diiodide **2** from dimesylate **6**

Entry	Solvent	Nal: <b>6</b> <sup>a</sup>	T <sup>b</sup> (°C)	t (d)	% Yield of <b>2</b> <sup>c</sup>
1 <sup>d,e</sup>	[bmim][BF <sub>4</sub> ]/CH <sub>3</sub> CN	10 (KI)	100	1	—
2 <sup>d,e</sup>	[bmim][BF <sub>4</sub> ]	10 (KI)	150	1	—
3 <sup>d,e</sup>	[bmim][BF <sub>4</sub> ]/ H <sub>3</sub> PO <sub>4</sub> 99%	20 (KI)	150	1	—
4 <sup>f</sup>	PMIMI	—	130	1	—
5	Tetrabutylammonium iodide	—	160	1	—
6	CH <sub>3</sub> SO <sub>3</sub> H (70%)	10	120	1	<5
7	H <sub>3</sub> PO <sub>4</sub> (99%)	40	170	1	46
8	H <sub>3</sub> PO <sub>4</sub> (99%)	40	150	3	52
9	H <sub>3</sub> PO <sub>4</sub> (99%)	60	150	1	72
10	H <sub>3</sub> PO <sub>4</sub> (99%)	100	150	1	73
11	H <sub>3</sub> PO <sub>4</sub> (99%)	200	150	1	75
12	H <sub>3</sub> PO <sub>4</sub> (99%)	16	150	2	54
13	H <sub>3</sub> PO <sub>4</sub> (99%)	40 (KI)	170	1	44
14	H <sub>3</sub> PO <sub>4</sub> (99%)	40 (CsI)	170	1	40
15 <sup>g</sup>	H <sub>3</sub> PO <sub>4</sub> (99%)	60	100	1	35
16 <sup>g</sup>	H <sub>3</sub> PO <sub>4</sub> (99%)	60	170	1	45
17 <sup>h</sup>	H <sub>3</sub> PO <sub>4</sub> (99%)	200	150	6 h	77
18 <sup>g</sup>	H <sub>3</sub> PO <sub>4</sub> (99%)	60	150	6 h	75

<sup>a</sup> Molar ratio of Nal to **6**. On a scale of 0.16 mmol of **6** unless otherwise specified.

<sup>b</sup> External bath temperature.

<sup>c</sup> Yield of crude product.

<sup>d</sup> bmim = 1-*n*-butyl-3-methylimidazolium.

<sup>e</sup> On a scale of 0.5 mmol of **6**.

<sup>f</sup> PMIMI = 1-methyl-3-propylimidazolium iodide.

<sup>g</sup> On a scale of 0.32 mmol of **6**.

<sup>h</sup> On a scale of 0.26 mmol of **6**.

accessible from diol **3**. Indirect iodination of **3** via dimesylate **6**, can be achieved within six hours in 60% overall yield. This indirect iodination method may be useful for other tertiary alcohols that do not form stable carbocations.

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- Synthesis of tricyclo[3.3.1.0<sup>3,7</sup>]nonane-3,7-diyl dimesylate (6)**. To a solution of diol **3** (1.00 g, 6.49 mmol) in pyridine (10 mL), mesyl chloride (CH<sub>3</sub>SO<sub>2</sub>Cl) (5.02 mL, 65 mmol) was added slowly with stirring at ambient temperature. The mixture was then heated at 120 °C for 5 h. After cooling, crushed ice (100 g) was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 × 20 mL). The combined organic phase was washed with 2 M HCl (2 × 40 mL), H<sub>2</sub>O (2 × 20 mL), saturated aqueous NaHCO<sub>3</sub> (2 × 20 mL), and dried (Na<sub>2</sub>SO<sub>4</sub>). After filtration and removal of the solvent under reduced pressure, a brown solid (1.92 g, 96%) was isolated. Recrystallization from THF/hexane afforded pure **6** (1.71 g, 85%) as colorless crystals, mp 127–128 °C; ν<sub>max</sub>(KBr) 3449, 2943, 1464, 1414, 1341, 1190, 1169, 1101, 1018, 976, 955, 856, 824, 802, 760, 669, 615, 565, 515, 474 cm<sup>-1</sup>; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 3.10 (6H, -CH<sub>3</sub>, s), 2.50 (6H<sub>(4eq+2CH)</sub>, d, J 6.9 Hz), 2.26 (4H<sub>ax</sub>, d, J 9.0 Hz), 1.51 (2H<sub>bridge</sub>, s); δ<sub>C</sub> (75.5 MHz, CDCl<sub>3</sub>) 91.30 (-CO), 47.42 (-CH<sub>2</sub>), 40.60 (-CH<sub>3</sub>), 34.98 (-CH), 32.28 (-CH<sub>2</sub> bridge). Anal. Calcd for C<sub>11</sub>H<sub>18</sub>O<sub>6</sub>S<sub>2</sub>: C, 42.6; H, 5.8; S, 20.7. Found: C, 42.3; H, 5.7; S, 20.3. HRMS (TOF MS ES+) calcd for C<sub>11</sub>H<sub>18</sub>O<sub>6</sub>S<sub>2</sub> 311.0623 found: 311.0629.
- Synthesis of 3,7-diiodo-tricyclo[3.3.1.0<sup>3,7</sup>]nonane 2<sup>5</sup>**. In a round-bottomed flask equipped with a reflux condenser, H<sub>3</sub>PO<sub>4</sub> (99%, 15 g), dimesylate **3** (80 mg, 0.26 mmol), and Nal (7.74 g, 52 mmol) were added. The mixture was stirred at 150 °C for 6 h. After cooling, H<sub>2</sub>O (100 mL) was added slowly to the mixture. The resulting purple solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 50 mL) and the combined organic phase was washed with aqueous sodium thiosulfate (1 × 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed under vacuum to give **2** (74 mg, 77%). Purification by dry flash chromatography (100% hexane) afforded **2** (69 mg, 72%) as colorless crystals, mp 130–131 °C; ν<sub>max</sub>(KBr) 2926, 1450, 1433, 1333, 1290, 1229, 1151, 1103, 1024, 970, 930, 903, 862, 849, 793, 770, 500 (C-I) cm<sup>-1</sup>; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 2.76 (4H<sub>eq</sub>, d, J = 12.0 Hz), 2.45 (4H<sub>ax</sub>, d, J = 10.8 Hz), 1.91 (2H, s, -CH), 1.63 (2H, s, -CH<sub>2</sub> bridge); δ<sub>C</sub> (75.5 MHz, CDCl<sub>3</sub>) 57.69 (-CH<sub>2</sub>), 53.34 (-Cl), 39.38 (-CH), 30.60 (-CH<sub>2</sub> bridge).
- In partially completed iodination reactions small amounts of 3-iodo-7-hydroxy-tricyclo[3.3.1.0<sup>3,7</sup>]nonane (**8**) were present. Compound **8** was isolated by chromatography (20% hexane/CH<sub>2</sub>Cl<sub>2</sub>) as a light-yellow crystalline solid: mp 52–54 °C; ν<sub>max</sub>(KBr) 3228 (O-H), 2930, 1722, 1454, 1398, 1344, 1331, 1300, 1244, 1215, 1184, 1136, 1109, 1063, 1007, 962, 937, 907, 870, 816, 718, 631, 520, 459, 422, 411; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 2.68 (2H<sub>eq-I</sub>, dd, J > 2, 12.9 Hz), 2.40 (2H<sub>ax-I</sub>, dd, J = 2.1, 11.1 Hz), 2.31 (2H, s, -CH), 2.10 (1H, s, -OH), 1.98 (2H<sub>eq-OH</sub>, dd, J > 2, 12.3 Hz), 1.88 (2H<sub>ax-OH</sub>, dd, J > 2, 10.8 Hz), 1.55 (2H, s, CH<sub>2</sub> bridge); δ<sub>C</sub> (75.5 MHz, CDCl<sub>3</sub>) 82.46 (-CO), 57.33 (-CH<sub>2</sub>), 54.62 (-Cl), 48.59 (-CH<sub>2</sub>), 37.92 (-CH), 31.69 (-CH<sub>2</sub> bridge).
- Synthesis of tricyclo[3.3.1.0<sup>3,7</sup>]nonane-3,7-diol cyclic sulfate 7**. Diol **3** (500 mg, 3.25 mmol) was added to concd H<sub>2</sub>SO<sub>4</sub> (95–97%, 5 mL) and the resulting mixture was stirred at 130 °C for 1 h. After cooling, H<sub>2</sub>O (100 mL) was added very slowly. The solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 20 mL), and the combined organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed under vacuum to give crude **7** (629 mg, 90%). Mp 117–118 °C; ν<sub>max</sub>(KBr) 2955, 2922, 2853, 1460, 1382, 1337, 1306, 1242, 1202, 1090, 960, 837, 812, 777; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 2.65 (2H, s, -CH), 2.32 (4H<sub>eq</sub>, d, J = 11.1 Hz), 2.19 (4H<sub>ax</sub>, d, J = 10.8 Hz), 1.55 (2H, s, -CH<sub>2</sub> bridge); δ<sub>C</sub> (75.5 MHz, CDCl<sub>3</sub>) 94.47 (C-O), 46.44 (CH<sub>2</sub>), 37.04 (CH), 33.00 (CH<sub>2</sub> bridge). Anal. Calcd for C<sub>9</sub>H<sub>12</sub>O<sub>4</sub>S: C, 50.0; H, 5.6; S, 14.8. Found: C, 50.4; H, 5.6; S, 14.4.
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