# Effective Synthetic Routes to Cubylcarbinol Derivatives

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**Abstract:** Three alternative routes for the synthesis of cubylcarbinol (**1**) from 4-iodocubanecarboxylic acid (**5**) are described.

**Key words:** cubane derivatives, 4-iodocubylcarbinol, cubylcarbinol, iodine removal

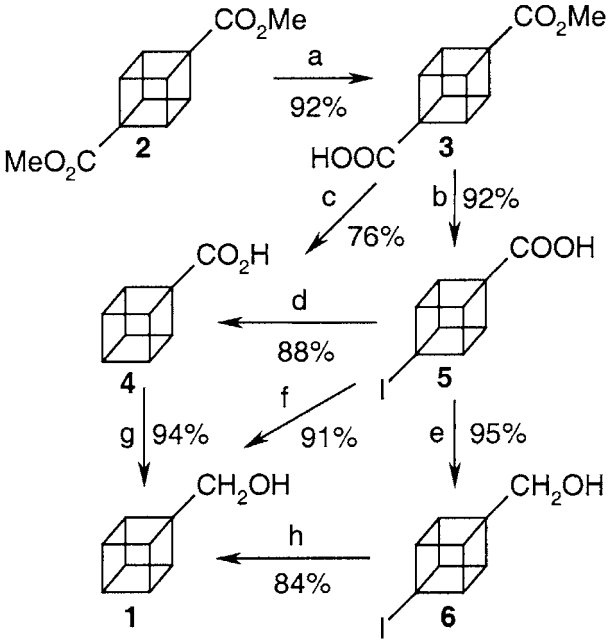
Since its initial synthesis in 1964,[1] cubane and cubyl compounds have been shown to be far more than just simple saturated hydrocarbons. From the potentially highly explosive (octanitrocubane)[2] to a multi-substituted analog with viral activity,[3] cubane derivatives have presented fascinating research challenges for decades. Monosubstituted cubane compounds have also shown some interesting properties, e.g. cubanol has been reported to go through an intramolecular rearrangement to open the cubane cage;[4] (aminomethyl)cubane shows enzyme activity.[5] The exocyclic bonds of cubanes have enhanced s-character[6] and we have recently demonstrated that dicubyl disulfide possesses the shortest known quaternary C–S bond length.[7] As part of our studies of convenient precursors for other cubane chemistry,[8] we needed synthetic procedures to prepare cubylcarbinol (**1**) in superior yields.

Cubylcarbinol (**1**) has previously been prepared in three steps from commercially available dimethyl-1,4-cubane dicarboxylate (**2**).[9] Partial hydrolysis of **2** yields 4-methoxycarbonylcubane carboxylic acid (**3**) which was converted to cubanecarboxylic acid (**4**) via a Barton decarboxylation followed by additional hydrolysis.[9a] Reduction of **4** affords cubylcarbinol (**1**).[9b] The best literature preparation delivers **1** in 70% overall yield from **2**. Herein, we report three alternative approaches to obtain **1** in excellent overall yield (Scheme 1).

From the 4-methoxycarbonyl cubane carboxylic acid (**3**), a Moriarty reaction[10] followed by hydrolysis of the unpurified intermediate yielded 4-iodocubanecarboxylic acid (**5**).

Three new avenues can be utilized for the synthesis of **1** from **5**. The removal of iodine from **5** with BuLi, followed by protonation with methanol delivers **4** in high yield (88%). Reduction of **4** with borane is analogous to that reported with $LiAlH_4$,[9b] producing **1** in identical yield (93–94%). Reduction of **5** with borane affords 4-(hydroxymethyl)-1-iodocubane (**6**).[11] The removal of iodine from **6** with BuLi, followed by protonation with methanol gave **1** in 84% yield (Scheme 1). However, what was initially surprising was the one-step reduction and iodine removal from **5** to give **1** in 91% yield using excess amounts of $LiAlH_4$ under reflux for an extended period of time.

Removal of halogens from tertiary carbons by $LiAlH_4$ has been reported in the past.[12] Ashby has carried out considerable research in this area and has shown that in some cases the reaction occurs via a single electron transfer (SET) mechanism[13] and in reactions of trityl halides, the trityl radical was detected using EPR spectroscopy.[14] We believe that in the conversion of **5** to **1** this is also the likely mode of reaction since a $S_N2$ mechanism is impossible and studies of the cubyl radical are well-documented.[15]




**Scheme 1** a) i. NaOH (1 equiv)–MeOH–THF, ii. HCl; b) i. IBDA, $I_2$–benzene, reflux 6 h, ii. NaOH–MeOH, iii. HCl; c) i. $(COCl)_2$–$CH_2Cl_2$, ii. 2-mercaptopyridine-*N*-oxide sodium salt hydrate, DMAP, *t*-BuSH–benzene, *hv*, iii. NaOH/MeOH, reflux, 1 h, iv. HCl; d) i. BuLi–THF, MeOH, –78 °C, ii. HCl; e) i. $BH_3{\cdot}SMe_2$–THF, 0 °C, ii. HCl; f) i. $LiAlH_4$ (50 equiv), THF, reflux, 5 d, ii. HCl; g) i. $BH_3{\cdot}SMe_2$–THF, 0 °C, ii. HCl; h) i. BuLi–THF, MeOH, –78 °C, ii. NaOMe, reflux, 1 h, iii. HCl

In contrast to the trityl halides where the reaction was completed in 5 hours with one equivalent of $LiAlH_4$, our system required 5 days, using 50 equivalents of $LiAlH_4$ under reflux conditions. A possible explanation for the extended time requirement is the fact that the carboxylic acid would first be reduced to the alkoxy anion providing

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a charged species that would not be very soluble in THF. This is supported by the fact that after 24 hours, the starting acid **5** was converted to a mixture of alcohols **6** and **1**.

We thus have a simple procedure to convert 4-iodocubanecarboxylic acid (**5**) into cubylcarbinol (**1**) in excellent yield. From **2**, we can obtain **1** in an overall yield of 77%. These routes provide a less expensive synthesis of **1** in addition to the fact that, depending upon the reducing agent employed, two different cubylcarbinols **1** and **6** can be obtained through the single precursor, **5**. In addition, **5** is a versatile intermediate, where it is possible to manipulate either the acid group[3,8,9b,11,16] and/or the iodo functionality.[7,11,17]

**4-Methoxycarbonylcubane Carboxylic Acid (3)**

This compound was prepared according to the literature procedure of Eaton.[9a]

Dimethyl 1,4-cubanedicarboxylate (**2**; 5.06 g, 23.0 mmol) yielded 4.33 g (92%) of 4-methoxycarbonylcubane carboxylic acid (**3**); mp 182–183 °C (Lit.[4,9a,18] mp 182–183 °C, 176–179 °C[19]).

$^1$H NMR (400 MHz, MeOD): δ = 3.69 (s, 3 H, $CH_3$), 4.19 (s, 6 H, cubyl H).

$^{13}$C NMR (100.6 MHz, MeOD): δ = 48.1, 48.2 (cubyl CH), 52.1 ($CH_3$), 57.4, 57.6 (cubyl C), 173.4 (C=O), 175.0 (C=O).

**4-Iodocubanecarboxylic Acid (5)**

Iodobenzene diacetate (IBDA, 18.32 g, 56.9 mmol) and $I_2$ (14.45 g, 56.9 mmol) were added to a suspension of 4-methoxycarbonylcubane carboxylic acid (**3**; 3.91 g, 19.0 mmol) in anhyd benzene (300 mL) under $N_2$. After refluxing for 7 h, the mixture was cooled to r.t., whereupon pentane (150 mL) was added. The solution was washed with sat. aq $Na_2SO_3$ (2 × 50 mL), $H_2O$ (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to near dryness. The red-brown liquid that remained was dissolved in THF (100 mL), and to it, NaOH (7.67 g, 19.2 mmol) dissolved in MeOH (75mL) and $H_2O$ (25 mL) was added and stirred overnight at r.t. The solution was evaporated to near dryness, dissolved in $H_2O$ (50 mL) and acidified with concd HCl (pH <1). The white precipitate was collected, and kept under vacuum to constant weight affording 4-iodocubanecarboxylic acid (**5**); yield: 4.76 g (92%); mp 215 °C (dec.) (Lit.[20] mp 174–178 °C).

$^1$H NMR (400 MHz, MeOD): δ = 4.23 (m, 3 H, H-2,6,8), 4.35 (m, 3 H, H-3,5,7).

$^{13}$C NMR (100.6 MHz, MeOD): δ = 37.0 (C-4), 51.2, 56.0 (cubyl CH), 57.9 (C-1), 174.8 (C=O).

**Cubanecarboxylic Acid (4) from 3**

This compound was prepared according to the literature procedure of Eaton.[9a]

4-Methoxycarbonylcubane carboxylic acid (**3**; 0.50 g, 2.4 mmol) yielded 0.27 g (76%) of cubanecarboxylic acid (**4**);[21] mp 124–125 °C (Lit.[1,9a] mp 124–125 °C).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.01 (m, 4 H, H-3,4,5,7), 4.28 (m, 3 H, H-2,6,8), 11.12 (s, 1 H, $CO_2H$).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = 45.2 (C-3,5,7), 47.9 (C-4), 49.5 (C-2,6,8), 55.3 (C-1), 117.8 (C=O).

**Cubanecarboxylic Acid (4) from 5**

To 4-iodocubanecarboxylic acid (**5**; 0.10 g, 0.37 mmol) dissolved in anhyd THF (50 mL) under $N_2$ at –78 °C, was added a 2.63 M solution of BuLi in hexanes (0.80 mL, 2.1 mmol). Cold MeOH (5 mL) was added after 5 min, and the solution was slowly allowed to reach r.t. Hexanes (25 mL) were added and the solution was extracted with $H_2O$ (3 × 50 mL). The aqueous layer was acidified to pH <1 with concd HCl, and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to dryness, affording pure cubanecarboxylic acid (**4**); yield: 0.05 g (88%); mp 124–125 °C (Lit.[1,9a] mp 124–125 °C).

**4-(Hydroxymethyl)-1-iodocubane (6)**

$BH_3$·$SMe_2$ complex (2.0 mL, 21 mmol) was added to a solution of 4-iodocubanecarboxylic acid (**5**; 3.62 g, 13.2 mmol) dissolved in anhyd THF (125 mL) under $N_2$ and cooled to 0 °C. The mixture was stirred at 0 °C for 20 min, then at r.t. for 4 h. The solution was quenched with $H_2O$ (20 mL) and stirred overnight. EtOAc (75 mL) was added and the organic layer was washed with $H_2O$ (2 × 50mL) and brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to dryness. Column chromatography ($CHCl_3$–EtOAc, 1:1) afforded 4-(hydroxymethyl)-1-iodocubane (**6**) as a white solid (3.25 g, 95%); mp 109–111 °C (Lit.[11] mp 108–110 °C).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, 1 H, OH), 3.78 (d, 2 H, $CH_2$), 4.05 (m, 3 H, H-3,5,7), 4.21 (m, 3 H, H-2,6,8).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 38.9 (C-1), 47.9 (C-2,6,8), 54.7 (C-3,5,7), 59.0 (C-4), 63.2 ($CH_2$).

**Cubylcarbinol (1) from 5**

$LiAlH_4$ (16.62 g, 438 mmol) was added to a solution of 4-iodocubanecarboxylic acid (**5**; 2.59 g, 9.46 mol) in anhyd THF (200 mL) under $N_2$ and refluxed for 5 d. The solution was cooled to 0 °C, and the mixture was *very*, *very* slowly quenched with cold MeOH. Once all the excess $LiAH_4$ was destroyed, the solution was acidified to pH <1 with concd HCl. Hexanes (200 mL) were added, and the organic layer was washed with $H_2O$ (3 × 200mL) and brine (150 mL), dried ($MgSO_4$), filtered, and evaporated to dryness. Column chromatography (hexanes–EtOAc, 3:1) afforded 1.16 g (91%) of cubylcarbinol (**1**); mp 62–63 °C (Lit.[9b] mp 62–62.5 °C).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, 1 H, OH), 3.72 (d, 2 H, $CH_2$), 3.89 (m, 6 H, H-2,3,5,6,7,8), 4.21 (m, 1 H, H-4).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = 44.6, 47.9 (cubyl CH), 48.9 (C-4), 58.6 (C-1), 64.1 ($CH_2$).

**Cubylcarbinol (1) from 4**

To a solution of cubanecarboxylic acid (**4**; 0.48 g, 3.2 mmol) dissolved in anhyd THF (50 mL) under $N_2$ at 0 °C was added $BH_3$·$SMe_2$ (0.50 mL, 5.3 mmol). After 20 min at 0 °C, the solution was warmed and stirred for an addition 2 h at r.t. The solution was quenched with $H_2O$ (10 mL) and stirred overnight. EtOAc (25 mL) was added, the organic layer was washed with $H_2O$ (2 × 20mL) and brine (20mL), dried ($MgSO_4$), filtered, and evaporated to dryness. Column chromatography (hexanes–EtOAc, 3:1) afforded 0.41 g (94%) of cubylcarbinol (**1**); mp 61–62 °C (Lit.[9b] mp 62–62.5 °C).

**Cubylcarbinol (1) from 6**

4-(Hydroxymethyl)-1-iodocubane (**6**; 0.32 g, 1.2 mmol) was dissolved in anhyd THF (50 mL) under $N_2$ and cooled to –78 °C, whereupon a 1.6 M solution of BuLi in hexanes (5.0 mL, 8.0 mmol) was added. After 25 min at –78 °C, cold MeOH (6 mL) was added and the solution was allowed to warm to r.t. and stirred for 1 h; 25wt% NaOMe in MeOH (5.6 mL) was added and the mixture was refluxed for 1 h. The solution was cooled, and hexanes (25 mL) were added. The organic layer was washed with $H_2O$ (2 × 25mL) and brine (25 mL), dried ($MgSO_4$), filtered, and evaporated. Column chromatography (hexanes–EtOAc, 3:1) afforded 0.13 g (84%) of cubylcarbinol (**1**); mp 59–61 °C (Lit.[9b] mp 62–62.5 °C).

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## References

(1) (a) Eaton, P. E.; Cole, T. W. Jr. *J. Am. Chem. Soc.* **1964**, *86*, 962. (b) Eaton, P. E.; Cole, T. W. Jr. *J. Am. Chem. Soc.* **1964**, *86*, 3157.
(2) (a) Service, R. F. *Science* **2000**, *287*, 564. (b) Zhang, M.-X.; Eaton, P. E.; Gilardi, R. *Angew. Chem. Int. Ed.* **2000**, *39*, 401. (c) Kortus, J.; Pederson, M. R.; Richardson, S. L. *Chem. Phys. Lett.* **2000**, *322*, 224. (d) Hrovat, D. A.; Borden, W. T.; Eaton, P. E.; Kahr, B. *J. Am. Chem. Soc.* **2001**, *123*, 1289.
(3) (a) Eaton, P. E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1421. (b) Mehrdad, M.; Sanjani, N. S. *Polym. Int.* **2000**, *49*, 260.
(4) Cole, T. W. Jr. *PhD Dissertation*; University of Chicago: USA, **1966**.
(5) Silverman, R. B.; Zhou, J. P.; Eaton, P. E. *J. Am. Chem. Soc.* **1993**, *115*, 8841.
(6) Della, E. W.; Hine, P. T.; Patney, H. K. *J. Org. Chem.* **1977**, *42*, 2940.
(7) Priefer, R.; Lee, Y. J.; Barrios, F.; Wosnick, J. H.; Lebuis, A.-M.; Farrell, P. G.; Harpp, D. N.; Sun, A.; Wu, S.; Snyder, J. P. *J. Am. Chem. Soc.* **2002**, *124*, 5626.
(8) Priefer, R.; Farrell, P. G.; Harpp, D. N. *Tetrahedron Lett.* **2002**, *43*, in press.
(9) (a) Eaton, P. E.; Nordari, N.; Tsanaktsidis, J.; Upadhyaya, S. P. *Synthesis* **1995**, 501. (b) Eaton, P. E.; Yip, Y. C. *J. Am. Chem. Soc.* **1991**, *113*, 7692.
(10) Moriarty, R. M.; Khosrowshahi, J. S.; Dalecki, T. M. *J. Chem. Soc., Chem. Commun.* **1987**, 675.
(11) Eaton, P. E.; Galoppini, E.; Gilardi, R. *J. Am Chem. Soc.* **1994**, *116*, 7588.
(12) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1982**, *47*, 276.
(13) Ashby, E. C.; Welder, C. O.; Doctorovich, F. *Tetrahedron Lett.* **1993**, *34*, 7235.
(14) Ashby, E. C.; DePriest, R. N.; Goel, A. B.; Wenderoth, B.; Pham, T. N. *J. Org. Chem.* **1984**, *49*, 3545.
(15) Luh, T.-Y.; Stock, L. M. *J. Org. Chem.* **1978**, *43*, 3271.
(16) Della, E. W.; Head, N. J. *J. Org. Chem.* **1995**, *60*, 5303.
(17) (a) Eaton, P. E.; Stossel, D. *J. Org. Chem.* **1991**, *56*, 5138. (b) Eaton, P. E.; Yang, C.-X.; Xiong, Y. *J. Am. Chem. Soc.* **1990**, *112*, 3225.
(18) Cole, T. W. Jr.; Mayers, C. J.; Stock, L. M. *J. Am. Chem. Soc.* **1974**, *96*, 4555.
(19) Edward, J. T.; Farrell, P. G.; Langford, G. E. *J. Am. Chem. Soc.* **1976**, *98*, 3075.
(20) Moriarty, R. M.; Khosrowshahi, J. S. *Synth. Commun.* **1989**, *19*, 1395.
(21) Instead of preparing the anhyd sodium salt of *N*-hydroxypyridine-2-thione from sodium omadine, we used commercially available 2-mercaptopyridine-*N*-oxide sodium salt hydrate.