# New Access to a Tricyclo[3.2.1.0$^{2,7}$]oct-3-ene Structure

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**Abstract:** A thermally induced reaction cascade including an electrocyclic rearrangement, two Diels–Alder reactions and a 1,4-elimination from a simple cyclobutene carbonate can explain the synthesis of a complex tricyclo[3.2.1.0$^{2,7}$]oct-3-ene core structure.

**Key words:** 1,4-elimination, Diels–Alder, electrocyclic reaction, polycycles, stereoselective synthesis

The strained tricyclo[3.2.1.0$^{2,7}$]oct-3-ene motif has been found as the core of a few molecules of biological interest[1] and in intermediate compounds in the synthesis of cafestol.[2] Among the most efficient ways to synthesize such an interesting structure are base-induced[3] or metal-catalyzed rearrangements,[4] the cobalt-catalyzed [4+2+2] cycloadditions,[5] the homo-Diels–Alder reactions[6] and the intramolecular Diels–Alder (IMDA) reactions.[7] This last method, involving the cyclization of a 5-vinyl-1,3-cyclohexadiene framework (Scheme 1) has been the most encountered and studied to date.

**Scheme 1**

We now report a route to a compound containing such a motif from methyl 3-phenylcyclobut-2-enyl carbonate (**5**) which was synthesized from phenyl acetylene (Scheme 2).

The 3-phenylcyclobutenone (**3**) was prepared following a procedure reported in the literature[8] except that the 3-phenyl-4,4-dichlorocyclobutenone (**2**) was not isolated prior to reduction. The cyclobutenone **3** was selectively reduced in high yield with sodium borohydride in methanol in the presence of cerium trichloride according to the Luche methodology[9] to the unstable allylic alcohol **4**.[10]

This species was immediately reacted with methyl chloroformate, triethylamine and 4-dimethylamino pyridine in dichloromethane to give the corresponding carbonate **5**[11] (Scheme 2) in 20% overall yield from phenyl acetylene in four steps.

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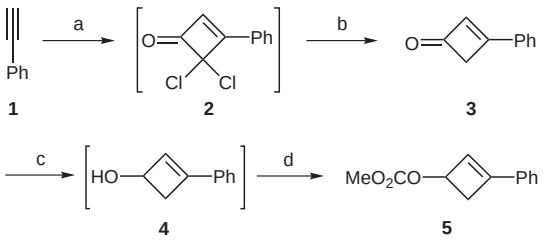
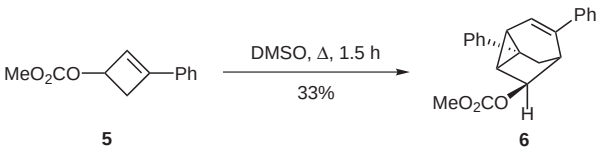



**Scheme 2** *Reagents and conditions*: (a) $CCl_3COCl$, Zn(Cu), DME, $Et_2O$; (b) Zn, TMEDA, AcOH, EtOH (39% from **1**); (c) *i.* $CeCl_3$, $NaBH_4$, MeOH, 10 min, r.t.; (d) $ClCO_2Me$, $Et_3N$, DMAP, $CH_2Cl_2$, r.t., 1.5 h (52% from **2**).




**Scheme 3**

Heating of compound **5** in refluxing DMSO for 90 minutes led to the formation of the tricyclic structure **6**[12] in 33% yield as a single diastereomer (Scheme 3) which was elucidated by extensive NMR studies including COSY, NOESY, HMQC and HMBC analysis.

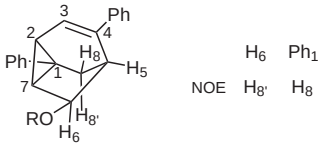



**Figure 1** Observed NOE for **6** (R = $CO_2Me$)

The NOE experiment, in particular, allowed the determination of the relative configuration at $C_6$ (Figure 1).

To confirm the unusual structure of this product, crystals were grown by slow diffusion of pentane into a dichloromethane solution of **6** and its structure (Figure 2) was determined by an X-ray diffraction study.

In order to elucidate the mechanistic nature of the transformation, we turned to reaction conditions with lower temperature. Compound **5** was heated at 140 °C in the absence of solvent for 30 minutes (Scheme 4) to give four products isolated by flash chromatography and a large

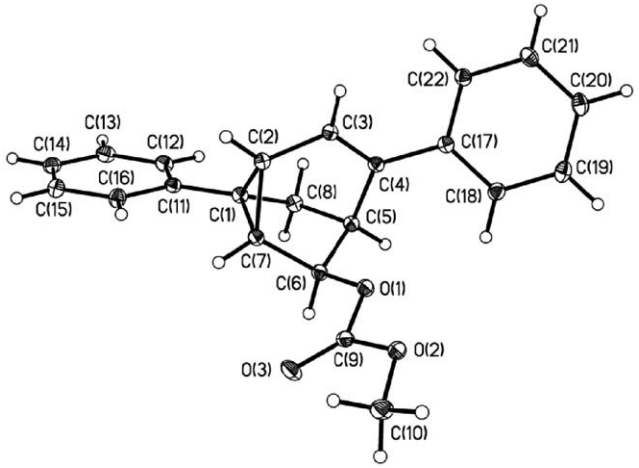
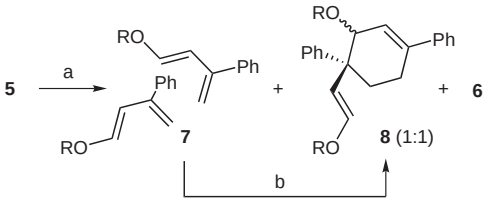


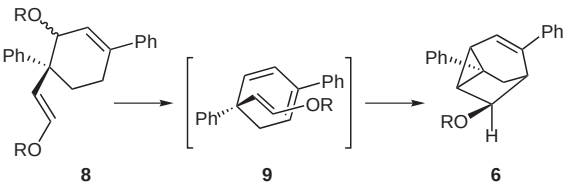

**Figure 2** X-ray crystal structure of compound **6**

amount of degradation.[13] The diene **7** (5%), resulting from a conrotatory ring opening[14] showed a doublet with a large coupling constant ($J$ = 12.4 Hz) at 7.09 ppm for the olefinic proton consistent with an *E*-configuration. An inseparable mixture of two diastereomers **8** (1:1; 19%) was characterized by NMR ($^1$H, $^{13}$C and DEPT) and HRMS while compound **6** was synthesized in 21% yield.




**Scheme 4** *Reagents and conditions*: (a) 140 °C, 30 min; (b) r.t., 3 months.

The $^1$H NMR spectra of a sample of diene **7** kept three months at room temperature showed the disappearance of this species with the formation of **8** (1:1) as the major products and, according to the presence of a multiplet between 3.9 and 3.4 ppm corresponding to the methoxy group, to degradation compounds. This totally regio- and chemoselective process thus allows for the formation of only two products out of eight possible stereoisomers.




**Scheme 5**

The logical missing link between **8** and **6** is the vinyl cyclohexadiene **9** (Scheme 5), which could arise from **8** through a rare thermal 1,4-elimination step,[15] and could cyclize via an IMDA reaction to furnish the tricyclic structure **6**. This compound was not isolated or detected in any analysis in this study and our attempt to generate it in basic conditions (*t*-BuOK, 18-crown-6 ether, toluene, r.t.) as reported in the literature for a similar compound[15] led to an intractable mixture. The IMDA process in that case is probably too rapid to allow the isolation of such a species. It is worth noting that the *E*-geometry of the dienophile part in **9** is required to deliver the OR group of compound **6** in the equatorial position. This configuration is observed in the precursors **7** (as mentioned above in the text) and **8** (both diastereomers had large coupling constants of 12.6 Hz and 12.7 Hz).

Both compounds **7** and **8** were refluxed in DMSO for 90 minutes to give **6** in 43% and 78% yields, respectively, indicating their participation as intermediate compounds on the route to the tricyclic structure.

In summary, we have reported the synthesis of a new substituted tricyclo[3.2.1.0$^{2,7}$]oct-3-ene structure from a simple cyclobutene carbonate. The yield of the overall transformation (33%) is high, taking into account the four steps involved in this one-pot process and the large number of possible diastereomers. A few other cyclobutene carbonates (where the phenyl group was replaced by alkyl or silyl substituents) were not transformed into the desired tricyclic species. We are now working on elucidating the nature of the substitution in order to expand these cascade reactions.

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(11) **Methyl 3-Phenylcyclobut-2-enyl Carbonate (5).**
To a solution of 3-phenylcyclobutenone (**3**, 2.1 g, 14.5 mmol) and $CeCl_3 \cdot 7H_2O$ (5.6 g, 22.7 mmol) in MeOH (50 mL) at r.t. was slowly added $NaBH_4$ (580 mg, 15 mmol) over 15 min. The reaction mixture was stirred at that temperature for 5 min, hydrolyzed with brine (50 mL) and extracted with $Et_2O$ (3 × 50 mL). The organic layer was dried over $MgSO_4$

and evaporated to give a residue (2.1 g) which was dissolved in $CH_2Cl_2$ (150 mL) in the presence of $Et_3N$ (8 mL, 57 mmol) and 4-dimethylamino pyridine (1 g, 8 mmol). Then, $ClCO_2Me$ (4.7 mL, 60 mmol) was slowly added and the reaction mixture was stirred for 75 min at r.t. After dilution in $CH_2Cl_2$ (50 mL), it was hydrolyzed with brine (100 mL) and extracted with $Et_2O$ (3 × 100 mL). The organic layer was dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography (pentane–$CH_2Cl_2$ = 70:30) to give the carbonate **5** as a yellow oil (1.83 g, 62%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.30 (m, 5 H), 6.34 (br s, 1 H), 5.40 (dt, *J* = 3.9, 1.0 Hz, 1 H), 3.81 (s, 3 H), 3.23 (ddd, *J* = 13.1, 3.9, 1.0 Hz, 1 H), 2.83 (dt, *J* = 13.1, 1.0 Hz, 1H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 155.4, 148.6, 133.0, 129.1, 128.4, 125.6, 125.0, 71.1, 54.6, 36.9 ppm. IR ($CHCl_3$): ν = 3062–2850, 1743, 1444, 1259 cm$^{-1}$. MS (EI): *m/z* = 146 [$MNH_4^+$ – $MeOCO_2H$].

(12) **Compounds 6**:
The carbonate **5** (300 mg, 1.5 mmol) in DMSO (1 mL) was heated at DMSO reflux for 1.5 h under argon. The crude reaction mixture was diluted with brine (15 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was dried over $MgSO_4$, evaporated and the residue was purified by flash chromatography ($CH_2Cl_2$–pentane = 1:2) to give the compound **6** as a white solid (84 mg, 33%). $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.20 (m, 10 H, arom.), 6.59 (dd, *J* = 6.2, 2.3 Hz, H$^3$), 5.26 (dd, *J* = 4.7, 2.3 Hz, 1 H, H$^6$), 3.71 (t, *J* = 3.9 Hz, 1 H, H$^5$), 3.69 (s, 3 H, H$^{10}$), 2.35 (dd, *J* = 6.8, 2.4 Hz, 1 H, H$^7$), 2.23 (dd, *J* = 8.0, 6.2 Hz, 1 H, H$^2$), 2.18 (dd, *J* = 11.7, 5.1 Hz, 1 H, H$^{8'}$), 1.57 (d, *J* = 11.7 Hz, 1 H, H$^8$) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 155.5 (C=O), 141.2 (Ph), 139.2 (C$^4$), 135.9, 127.5, 126.7, 126.2, 126.0, 124.9 (Ph), 120.4 (C$^3$), 75.5 (C$^6$), 54.5 (methoxy), 38.3 (C$^5$), 31.9 (C$^1$), 31.2 (C$^8$), 28.2 (C$^2$), 27.2 (C$^7$) ppm. Mp 117 °C. IR (KBr): 3031, 2922, 2856, 1742, 1440, 1292, 1265, 968, 755, 697 cm$^{-1}$. Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.50; H, 6.31.

(13) The carbonate **5** (368 mg, 1.8 mmol) was heated at 140 °C (neat) for 30 min. The residue was purified by flash chromatography (pentane–$Et_2O$ = 95:5, followed by pentane–$Et_2O$ = 80:20) to afford successively the tricyclic compound **6** as a white solid (62 mg, 21%), a mixture of the diastereomers **8** (69 mg, 19%) and diene **7** (10 mg, 5%).
Diastereomers **8**: $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.20 (m, 20 H, Ph), 6.95 (d, *J* = 12.6 Hz, 1 H, $CH_{trans}$), 6.91 (d, *J* = 12.7 Hz, 1 H, $CH_{trans}$), 6.32 (br d, *J* = 5.1 Hz, 1 H, CH), 6.29 (dt, *J* = 4.3, 1.6 Hz, 1 H, CH), 5.73 (d, *J* = 12.6 Hz, 1 H, $CH_{trans}$), 5.65 (d, *J* = 4.3 Hz, 1 H, CHO), 5.63 (d, *J* = 12.7 Hz, 1 H, $CH_{trans}$), 5.51 (d, *J* = 5.1 Hz, 1 H, CHO), 3.82 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 3.55 (s, 3 H, OMe), 2.70–2.40 (m, 4 H, $CH_2$), 2.40–2.10 (m, 4 H, $CH_2$) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 155.4, 155.0, 153.4, 153.3 (CO), 142.9, 142.2, 142.1, 142.0 ($C_{ipso}$), 140.1, 140.0 ($C_Q$), 138.9, 138.4 (CH), 128.4, 128.3, 128.2, 128.1, 127.9, 127.3, 126.9, 126.8, 126.7, 125.6, 125.5, 120.6, 119.5, 118.9, 118.7 (CH), 77.2, 75.7 (CH), 55.2, 55.1, 54.8, 54.6 ($CH_3$), 44.4, 44.1 ($C_Q$), 29.7, 27.7, 25.5, 25.1 ($CH_2$) ppm. HRMS: *m/z* calcd for $C_{24}H_{28}O_6N$ [M + $NH_4$]: 426.1917; found: 426.1915.
Diene **7**: $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 12.4 Hz, 1 H), 6.32 (dd, *J* = 12.4, 0.8 Hz, 1 H), 5.27 (dd, *J* = 1.5, 0.6 Hz, 1 H), 5.15 (d, *J* = 1.5 Hz, 1 H), 3.84 (s, 3 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 153.3, 143.6, 140.3, 139.5, 128.4, 127.8, 117.2, 116.5, 55.3 ppm. MS (EI): *m/z* = 178 [$MNH_4^+$ – $CO_2$].

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