# Three step syntheses of naphthofurans and phenanthrofurans related to (−)-morphine from *ortho*-benzoquinone monoketals by Diels–Alder and Cope reactions

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**Adducts of the intramolecular Diels–Alder reaction of *o*-benzoquinone monoketals are rapidly converted to oxygen heterocycles *via* Cope rearrangements.**

The considerable synthetic potential of *ortho*-benzoquinonoid monoketals remains largely unexploited despite a few noteworthy applications[1] in natural product synthesis. Our laboratory has recently embarked on a program to study the inter-[2] and intra-molecular Diels–Alder (IMDA) reactions[3] of such intermediates and to evaluate the synthetic utility of the resulting adducts. We recently reported[3] the Cope rearrangement of one adduct and its use in a brief and efficient synthesis of the pentacyclic marine sponge metabolite (±)-Xestoquinone. The success of this two step IMDA–Cope sequence has prompted us to explore the Cope rearrangements of several additional bridged IMDA adducts to demonstrate their generality and illustrate their value with a convergent three-step route to a 3-hydroxy-9c-allylphenanthro[4,5-*bcd*]furan **14b** constituting rings A, B, C and E of morphine.[4]

Each of four substituted guaiacols **1a**–**d** were treated with a minimum of 5 equiv. of (*E*)-penta-2,4-dienol in the presence of bis(trifluoroacetoxy)iodobenzene (BTIB), to provide the mixed monoketals **2** that reacted *in situ* to generate the IMDA adducts **3** and **4** in combined yields of 53–88% (Table 1 and Scheme 1). After separation of the adducts, thermal Cope rearrangements of the bridged compounds **3a**–**f** were effected (Table 2).[5] Several naphtho[1,8-*bc*]furan tricycles **4a**, **b**, **e**, **f**, all *endo*† isomers and bearing a carbon substituent ($R^3$) at a ring junction, are thus obtainable in two steps from simple starting materials. Bridged adduct **3e** generated the naphthofuran **7e** upon heating in aromatic hydrocarbon solvents (entries 8 and 9). This is presumably the result of a facile dienone–phenol rearrangement of intermediate **5e**. We have observed that thiol esters like **5e** are particularly prone to such migrations. Acid-catalysed elimination of MeOH (using TFA) from **4f**, and subsequent alkaline hydrolysis of the ester, produced the phenol **7** ($R^1$ = $R^3$ = H) after spontaneous decarboxylation (90%).‡

The tetracyclic phenanthrofuran system is also readily accessible by application of the same chemistry. The reaction of methyl vanillate **1f** with 3 equiv. of 3-vinylcyclohex-2-enol[6] **9a** produced a mixture of *exo* (**10a**) and *endo* (**11a**) IMDA adducts, together with a small amount of the bridged adduct **12a** (Scheme 2). X-Ray crystal structures§ of **10a** and **11a** were obtained to establish their structure and relative configurations.

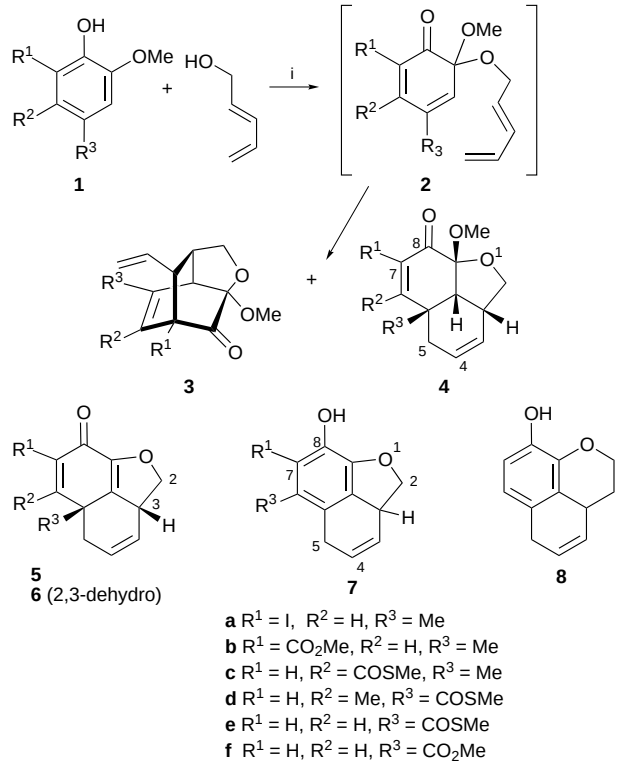
**Table 1** Diels–Alder reactions of guaiacols **1** with (*E*)-penta-2,4-dienol

| Substituted guaiacol[a] | Products (% yield) |
|---|---|
| **1a** | **3a** (72), **4a** (16) |
| **1b** | **3b** (65), **4b** (13) |
| **1c** | **3c** (65), **4c** (7) |
| **1d** | **3d** (52), **4d** (1) |

[a] For three more examples, see ref. 3.

The *endo* isomer (**11a**) was easily aromatized in two steps: brief treatment with TFA to eliminate MeOH produced the dienone **13a** (92%), and saponification of the ester resulted in spontaneous decarboxylation and aromatization to **14a** (90%). The ketal moiety of the *exo* isomer (**10a**) was remarkably stable to prolonged acid treatment at room temperature.

It is generally acknowledged that acid hydrolysis of an acetal is promoted by the presence of at least one non-bonded electron pair on the endocyclic oxygen atom in an antiperiplanar relationship with the exocyclic carbon–oxygen bond that is being cleaved in the reaction.[7] Furthermore, the relationship between C–O bond lengths and O–C–O angles of acetals in the ground state and the ease of acid-catalysed hydrolysis has been convincingly demonstrated.[8,9] The relevant bond lengths and angles of **10a** and **11a** are shown in Table 3, together with projections along the O(4)–C(3a) bond derived from the X-ray structures (Fig. 1), with the non-bonding $sp^3$ orbitals of O(4) added in approximately tetrahedral orientations. These projections clearly show that the stereoelectronic requirements for the acid-catalysed elimination of MeOH can only be met in the *endo*-adduct **11a**, and this is reflected in the corresponding changes in bond lengths of C(3a)–OMe (longer) and C(3a)–O(4) (shorter), exactly opposite to the situation in the *exo*-

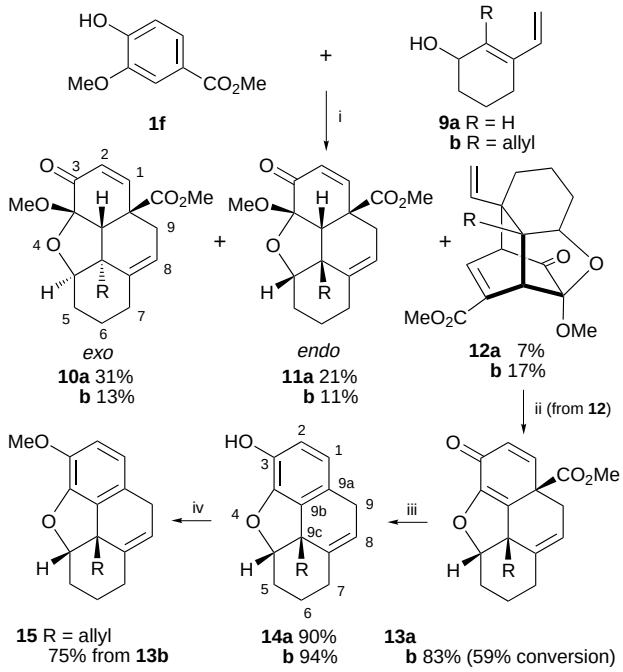



**Scheme 1** *Reagents and conditions*: i, BTIB, THF, 0 °C

**Table 2** Thermal Cope rearrangements of bridged IMDA adducts **3** in various solvents

| Entry | Reactant | Solvent[a] (% conversion) | Products (% yield) |
|---|---|---|---|
| 1 | **3a** | TMB[a] (100) | **4a** (38)[b] |
| 2 | **3a** | Decane[c] (100) | **6a** (50) |
| 3 | **3a** | TCE[a] (61) | **6a** (70) |
| 4 | **3b** | TCE[c] (100) | **4b** (10), **6b** (32) |
| 5 | **3c** | Decane[c] (72) | **6c** (25) |
| 6 | **3d** | Decane | Decomposition product |
| 7 | **3e**[d] | Decane (84) | **4e** (81) |
| 8 | **3e**[d] | *p*-Xylene (100) | **4e** (6), **7e** (28) |
| 9 | **3e**[d] | TMB (100) | **7e** (42) |
| 10 | **3f**[d] | TMB (100) | **4f** (46), **5f** (20) |
| 11 | **3f**[d] | *p*-Xylene (93) | **4f** (21), **5f** (44) |

[a] TMB = 1,2,4-trimethylbenzene; TCE = 1,1,2,2-tetrachloroethane. [b] Iodine was also produced. [c] Some thermal rearrangements performed in decane and TCE resulted in significant decomposition. [d] For the preparation of **3e** and **3f**, see ref. 3.




**Scheme 2** *Reagents and conditions*: i, BTIB; ii, $Cl_2CHCHCl_2$, heat; iii, NaOH, MeOH; iv, $K_2CO_3$, $Me_2SO_4$, acetone

**Table 3** Bond lengths and angles at the C(3a) ketal carbon atom of **10a** and **11a**

| | Bond length/Å | | |
|---|---|---|---|
| | C(3a)–O(4) | C(3a)–OMe | Bond angle (°) O(4)–C(3a)–OMe |
| **10a** (*exo*) | 1.422 | 1.401 | 109.1 |
| **11a** (*endo*) | 1.407 | 1.416 | 111.6 |

adduct **10a**. The reluctance of the latter adduct to undergo the elimination can thus be understood.

The 2-allylcyclohexenol **9b**, prepared from 2-allylcyclohexane-1,3-dione[10] in a similar manner to **9a**, reacted with methyl vanillate **1f** to provide a mixture of three adducts **10b**, **11b** and **12b** (Scheme 2). Again, the *exo*-adduct **10b** was stable to acid while the *endo*-isomer **11b** was converted to dienone **13b** by brief exposure to TFA. When the bridged adduct **12b** was subjected to the thermal Cope rearrangement in refluxing 1,1,2,2-tetrachloroethane, elimination of MeOH also occurred

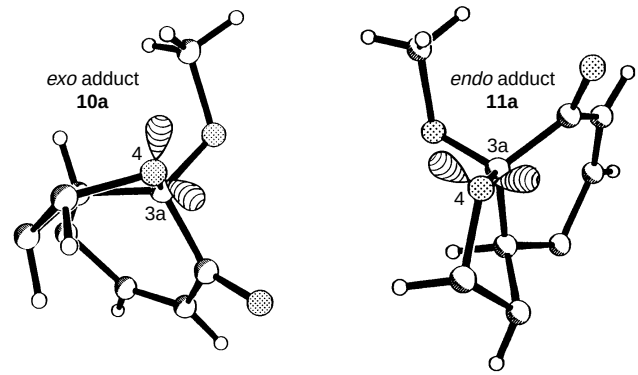



**Fig. 1** Projections along the C(3a)–O(4) bonds adapted from X-ray structures of **10a** and **11a**

to produce **13b** (83% yield, 59% conversion), which was saponified as before to produce **14b** (94%).

Reduction of 2-allyl-3-vinylcyclohex-2-enone with borane and 20 mol% of the (*R*)-oxazaborolidine[11] provided the (*S*)-(−)-cyclohexenol **9b** in 84% yield and 88% ee.¶ Repetition of the same sequence of reactions with (−)-**9b** afforded **15**, the methyl ether of phenol **14b** in 75% yield (88% ee) from **13b**. Further progress in the conversion of **14b** or **15** to a morphinan[12] will be reported in due course.‖

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## Footnotes and References

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† The terms *exo* and *endo* are used with respect to the *o*- quinonoid ring.

‡ The same sequence of reactions was also used to generate the naphtho[1,8-*bc*]pyran system **8** from methyl vanillate and hexa-3,5-dienol.

§ *Crystal Data* for **10a**: Colourless plate of $C_{17}H_{20}O_5$, triclinic, space group $P\bar{1}$, $M$ = 304.3, $a$ = 7.8603(8), $b$ = 7.9599(8), $c$ = 12.6351(11) Å, $\alpha$ = 103.516(5), $\beta$ = 104.685(5), $\gamma$ = 100.226(7)°, $V$ = 719.6(2) Å$^3$, $Z$ = 2, $T$ = 160 K, $w^{-1} = \sigma^2(F) + 0.00007F^2$, $wR$ (all data) = 5.02%, $wR$ (obs. data) = 4.97%. For **11a**: Colourless needle prism fragment of $C_{17}H_{20}O_5$, orthorhombic, space group *Pbca*, $M$ = 304.3, $a$ = 23.109(3), $b$ = 10.525(1), $c$ = 12.005(2) Å, $V$ = 2919.9(8) Å$^3$, $Z$ = 8, $T$ = 160 K, $w^{-1} = \sigma^2(F)$, $wR$ (all data) = 3.80%, $wR$ (obs. data) = 3.74%. CCDC 182/672.

¶ The enantiomeric excesses of **9b** and **15** were determined in each instance by HPLC separation on a Chiralcel OD column using hexane–isopropanol.

‖ All new compounds prepared in this study provided satisfactory spectroscopic data. Full details will be published later.

1 P. Deslongchamps, *Pure Appl. Chem.*, 1977, **49**, 1329; S. Yamamura, Y. Shizumi, H. Shigemori, Y. Okuno and M. Okhubo, *Tetrahedron*, 1991, **47**, 635; T. H. Lee, C.-C. Liao and N. C. Liu, *Tetrahedron Lett.*, 1996, **37**, 5897.
2 R. Carlini, C.-L. Fang, D. Herrington, K. Higgs, R. Rodrigo and N. Taylor, *Aust. J. Chem.*, 1997, **50**, 271.
3 R. Carlini, K. Higgs, C. Older, S. Randhawa and R. Rodrigo, *J. Org. Chem.*, 1997, **62**, 2330.
4 For recent syntheses of morphinans, see J. Mulzer, J.W. Bats, B. List, T. Opatz and D. Trauner, *Synlett*, 1997, 441 and references cited therein.
5 A Cope rearrangement of an intermolecular adduct of cyclopentadiene with an *o*-benzoquinone has been reported; M. F. Ansell, A. F. Gosden, V. J. Leslie and R. A. Murray, *J. Chem. Soc.* (*C*), 1971, 1041.
6 E. J. Corey and A. G. Meyers, *Tetrahedron Lett.*, 1984, **25**, 3559.
7 P. Deslongchamps, in *Stereoelectronic Effects in Organic Chemistry*, Pergamon Oxford, 1983.
8 P. G. Jones and A. J. Kirby, *J. Chem. Soc., Chem. Commun.*, 1979, 288.
9 H. B. Bürgi, J. D. Dunitz and E. Shefter, *Acta Crystallogr.*, 1974, **B30**, 1517; P. G. Jones, O. Kennard, S. Chandrasekhar and A. J. Kirby, *Acta Crystallogr.*, 1978, **B34,** 3835.
10 H. Stetter and W. Dierichs, *Chem. Ber.*, 1952, **85**, 1061.
11 E. J. Corey, P. Da Silva Jardine and T. Mohri, *Tetrahedron Lett.*, 1988, **29**, 6409.
12 T. Hudlicky, C. H. Boros and E. E. Boros, *Synthesis*, 1992, 174.

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