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A facile Diels–Alder route to dihydronaphthofuranones

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Abstract

An efficient, multigram-scale synthesis of dihydronaphthofuranone **1** using a novel aryl intramolecular Diels–Alder reaction of propargyl *trans*-cinnamate **8** is described. Catalytic reduction of **1** gave the *cis*-fused tetrahydronaphthofuranone derivative **2**.

Keywords: dihydronaphthofuranone; tetrahydronaphthofuranone; perhydronaphthofuranone; intramolecular Diels–Alder reaction; aryl intramolecular Diels–Alder reaction.

The naphthofuranone ring system is found in a number of biologically important natural products such as podophyllotoxin (**3**), conidendrin (**4**), and himbacine (**5**) (Fig. 1).[1–4] The stereoselective construction of tetrahydro- and perhydronaphthofuranone skeletons often requires lengthy protocols.[5,6] In connection with the total synthesis of himbacine, we have reported an efficient intramolecular Diels–Alder (IMDA) reaction (Eq. (1)) that leads to the stereoselective construction of perhydronaphthofuranone ring system.[6a,7,8] Herein we wish to report the extension of this methodology to the construction of functionalized tetrahydronaphthofuranones using a novel aryl intramolecular Diels–Alder reaction as represented in Eq. (2).

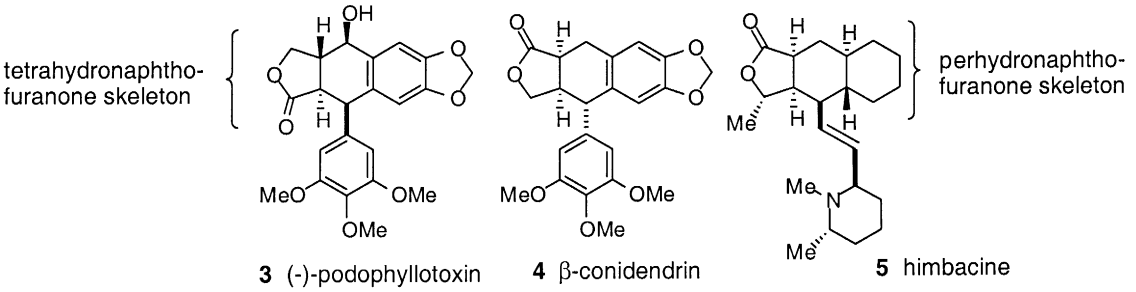

Fig. 1.

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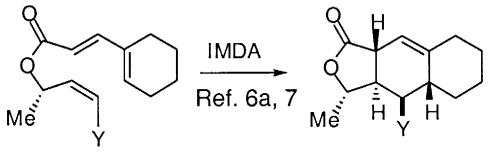
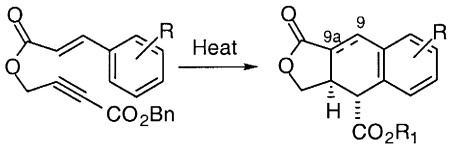
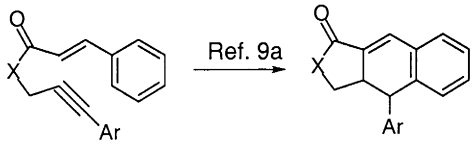


6 Y = alkenyl, alkynyl, carbonyl[8] **7** (1)

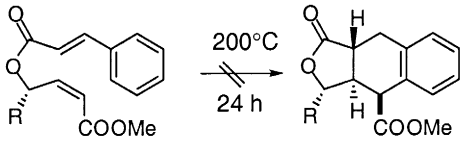


8 **1** 9, 9a = olefin; R_1 = Bn
2 9, 9a-α = H_2; R_1 = H (2)

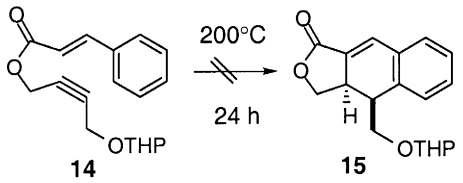
Klemm has reported the intramolecular Diels–Alder cyclization of cinnamamide derivatives **9** (Eq. (3)).[9] However, these examples are limited to phenyl propargyl cinnamamides (**9**). Attempted cyclization of the corresponding ester **11** has been reportedly unsuccessful.[9a] Our own attempts to cyclize cinnamate derivatives **12** and **14** resulted only in the recovery of unreacted starting material. However, we have found that the cinnamic acid ester **8**, which contains an activated propargylic moiety as the dienophile, undergoes efficient cyclization at 195°C to give the tricyclic dihydronaphthofuranone intermediate **1** (Eq. (2)).



9 X = *N*-alkyl
11 X = O No reaction[9a] **10** (3)

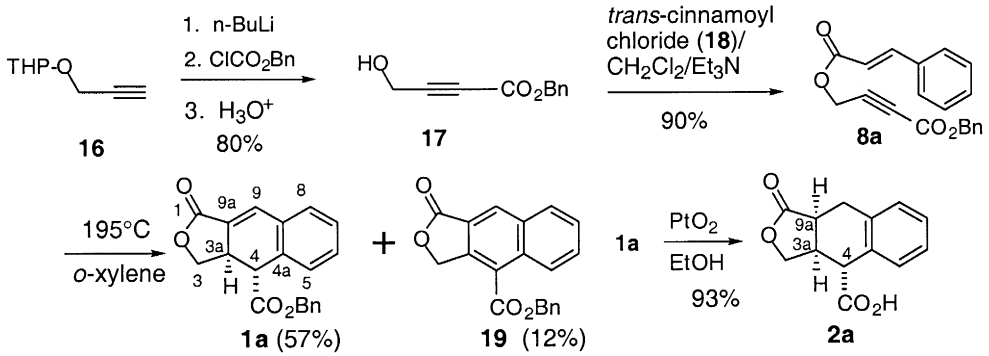


12 R = Me or H **13** (4)



14 **15** (5)

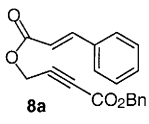
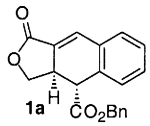
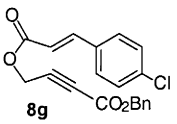
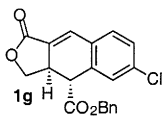
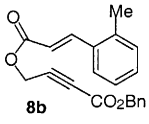
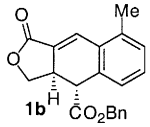
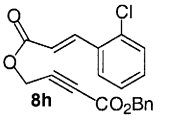
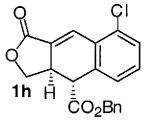
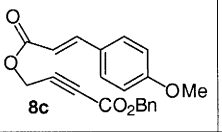
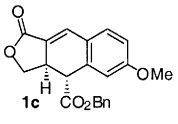
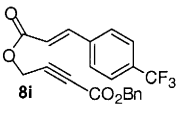
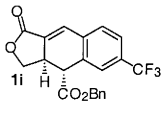
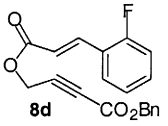
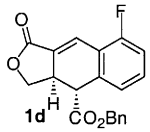
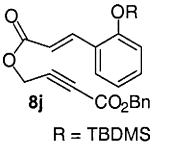
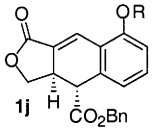
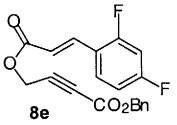
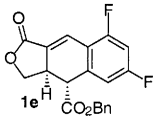
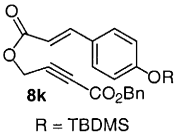
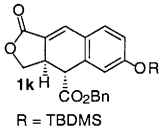
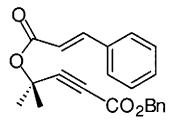
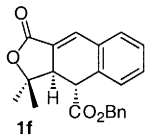
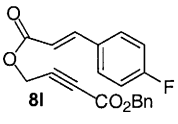
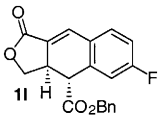
The general synthetic approach is presented in Scheme 1. Esterification of commercially available cinnamoyl chloride (**18**) with the propiolate **17**, prepared in two steps from commercially available protected propargylic alcohol **16**, yielded the IMDA precursor **8a**. The cyclization was effected by heating a solution of **8a** in *o*-xylene for 24 h to give the tricyclic derivative **1a**. A small quantity (10–15%) of naphthofuranone **19** was isolated as the side product. Rigorous exclusion of oxygen and a shorter reaction time minimized the relative amount of this side product, which presumably arises from the air oxidation of **1a**. A single diastereomer of the product, with exclusive presence of the double bond at the C_9–C_{9a} position, was isolated in all cases.



Scheme 1.

As shown in Table 1, the reaction is general for a variety of substrates and can be readily performed on a 100 g scale. The unoptimized yields generally range between 45 and 65%. The versatility of this process is further underscored by the ease with which the Diels–Alder precursor is synthesized from commercially available cinnamoyl chlorides (Scheme 1). Catalytic hydrogenation of dihydronaphthofuranone **1a**

Table 1

Substrate	Product	Yield	Substrate	Product	Yield
 8a	 1a	57%	 8g	 1g	66%
 8b	 1b	47%	 8h	 1h	57%
 8c	 1c	50%	 8i	 1i	42%
 8d	 1d	48%	 8j R = TBDMS	 1j R = TBDMS	59%
 8e	 1e	47%	 8k R = TBDMS	 1k R = TBDMS	50%
 8f	 1f	54%	 8l	 1l	47%

yielded the *cis*-fused[10,11] tetrahydronaphthofuranone carboxylic acid **2a** (Fig. 2) which is potentially a versatile intermediate for the synthetic exploration of some of the natural products mentioned above and the structure–activity relationship (SAR) studies of their analogs.

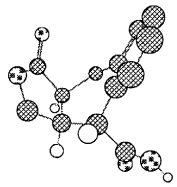


Fig. 2. X-Ray crystallographic structure of **2a** (hydrogen atoms shown only at C_{9a}, C_{3a}, and C_4)

In summary, we have discovered a concise synthesis of functionalized dihydronaphthofuranone derivatives in three steps using a novel aryl intramolecular Diels–Alder reaction of cinnamic acid esters. Further application of this methodology in the synthesis of biologically active compounds and the mechanistic aspects of this aryl intramolecular Diels–Alder reaction will be reported in the future.

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8. Carbonyl activation of dienophile in the precursor **6** gives an excellent outcome of the intramolecular Diels–Alder reaction, although this result has not been reported in Ref. 6a and 7.
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10. The relative stereochemistry of cyclization product **1a**, initially established using NMR methods, was corroborated by X-ray crystallographic analysis of the crystalline carboxylic acid **2a** (Fig. 2).
11. Representative physical data: Compound **8a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (s, 2H), 5.22 (s, 2H), 6.51 (d, J=16.0 Hz, 1H), 7.41–7.50 (m, 8H), 7.59–7.61 (m, 2H), 7.81 (d, J=16.0 Hz, 1H); IR (neat) 1716, 1635 cm^{-1}. Compound **1a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58–3.68 (m, 1H), 3.86 (d, J=15.0 Hz, 1H), 4.04 (t, J=9.0 Hz, 1H), 4.64 (t, J=9.0 Hz, 1H), 5.31 (d, J=12.0 Hz, 1H), 5.38 (d, J=12.0 Hz, 1H), 7.16–7.21 (m, 2H), 7.29–7.45 (m, 8H); IR (neat) 1785, 1735 cm^{-1}; MS (ESI) *m/e* 321 $(M+H)^+$. Compound **8c**: ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H), 4.91 (s, 2H), 5.21 (s, 2H), 6.30 (d, J=15.6 Hz, 1H), 6.91 (d, J=6.8 Hz, 2H), 7.38 (m, 5H), 7.48 (d, J=7.2 Hz, 2H), 7.70 (d, J=16 Hz, 1H); MS (ESI) *m/e* 351 $(M+H)^+$. Compound **1c**: ^{1}H NMR ($CDCl_3$) δ 3.59 (m, 1H), 3.65 (s, 3H), 3.82 (d, J=11 Hz, 1H), 4.02 (t, J=8.8 Hz, 1H), 4.64 (t, J=8.95 Hz, 1H), 5.27 and 5.40 (dd, J=12.0 Hz, 2H), 6.73 (s, 1H), 6.83 (d, J=1.6 Hz, 1H), 7.29 (d, J=4.8 Hz, 1H), 7.49 (m, 6H); MS (ESI) *m/e* 351 $(M+H)^+$. Compound **8d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.93 (s, 2H), 5.22 (s, 2H), 6.55 (d, J=16.0 Hz, 1H), 7.11

(t, *J*=8.0 Hz, 1H), 7.17 (t, *J*=8.0 Hz, 1H), 7.35–7.40 (m, 6H), 7.53 (td, *J*=8.0 Hz, 2.0 Hz, 1H), 7.87 (d, *J*=16.0 Hz, 1H); MS (FAB) *m/e* 339 $(M+H)^+$; anal. calcd for $C_{20}H_{15}FO_4$: C, 71.00; H, 4.47. Found: C, 70.66; H, 4.51. Compound **1d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.58–3.65 (m, 1H), 3.84 (d, *J*=15.0 Hz, 1H), 4.05 (t, *J*=9.0 Hz, 1H), 4.65 (t, *J*=9.0 Hz, 1H), 5.31 (d, *J*=12.0 Hz, 1H), 5.37 (d, *J*=12.0 Hz, 1H), 6.97 (d, *J*=8.0 Hz, 1H), 7.05 (t, *J*=8.0 Hz, 1H), 7.24–7.31 (m, 1H), 7.35–7.42 (m, 5H), 7.72 (d, *J*=3.0 Hz, 1H); MS (FAB) *m/e* 339 $(M+H)^+$; anal. calcd for $C_{20}H_{15}FO_4 \cdot 0.78CH_2Cl_2$: C, 61.69; H, 4.13. Found: C, 61.62; H, 4.43. Compound **8l**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.92 (s, 2H), 5.22 (s, 2H), 6.36 (d, *J*=16.0 Hz, 1H), 7.10 (t, *J*=9.0 Hz, 2H), 7.36–7.39 (m, 5H), 7.50–7.54 (m, 2H), 7.70 (d, *J*=16.0 Hz, 1H); IR (neat) 1713 cm^{-1}; MS (FAB) *m/e* 339 $(M+H)^+$; anal. calcd for $C_{20}H_{15}FO_4$: C, 71.00; H, 4.47. Found: C, 70.60; H, 4.46. Compound **1l**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.58–3.65 (m, 1H), 3.84 (d, *J*=15.0 Hz, 1H,), 4.04 (t, *J*=9.0 Hz, 1H), 4.65 (t, *J*=9.0 Hz, 1H), 5.32 (d, *J*=12.0 Hz, 1H), 5.38 (d, *J*=12.0 Hz, 1H), 6.95–7.04 (m, 2H), 7.33–7.43 (m, 7H); IR (neat) 1756, 1739, 1727 cm^{-1}. MS (ESI) *m/e* 339 $(M+H)^+$; anal. calcd for $C_{20}H_{15}FO_4$: C, 71.00; H, 4.50. Found: C. 70.70; H, 4.50.