

# A Novel and Facile Synthesis of Functionalized [4.4.3] and [4.4.4]Propellano-bislactones Using Acetates of the Baylis–Hillman Adducts

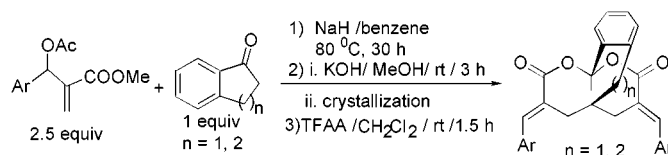
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Received July 20, 2001

## ABSTRACT



A simple and convenient synthesis of 11,16-di[(*E*)-arylidene]-13,14-dioxatetracyclo-[7.4.4.0.<sup>1,9</sup>0<sup>2,7</sup>]heptadeca-2,4,6-triene-12,15-diones and 12,17-di[(*E*)-benzylidene]-14,15-dioxatetracyclo[8.4.4.0.<sup>1,10</sup>0<sup>2,7</sup>]octadeca-2,4,6-triene-13,16-dione, i.e., 2,10-dioxo[4.4.3]propellane-3,9-diones and 2,10-dioxo[4.4.4]propellane-3,9-dione, using acetates of the Baylis–Hillman adducts has been described.

Carbocyclic and heterocyclic propellanes occupy a special place in synthetic organic chemistry because of their aesthetically appealing structural architecture.<sup>1</sup> The polycyclic polylactone framework is an important structural feature present in various biologically active and natural products.<sup>2</sup> The beautiful structural architecture of propellanes and important biological properties of polylactones have attracted our attention, and we herein report a simple and convenient methodology for synthesis of functionalized propellano-bislactones<sup>3</sup> using acetates of the Baylis–Hillman adducts.

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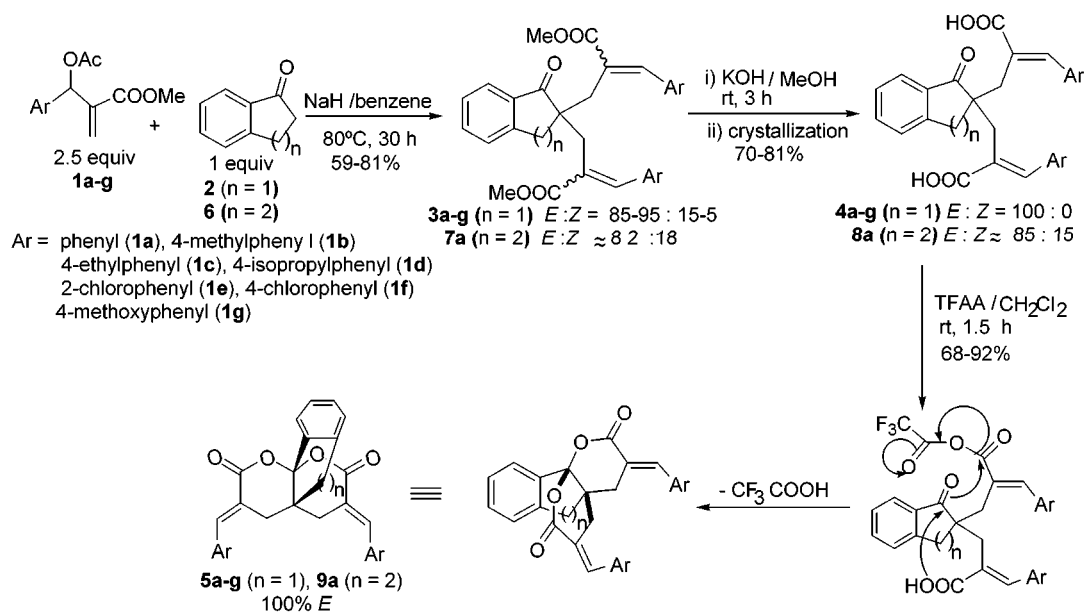
In recent years the Baylis–Hillman carbon–carbon bond forming reaction has attracted the attention of organic chemists as this reaction provides densely functionalized molecules that have been used in a variety of interesting organic transformations.<sup>4–6</sup> In continuation of our interest

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## Scheme 1



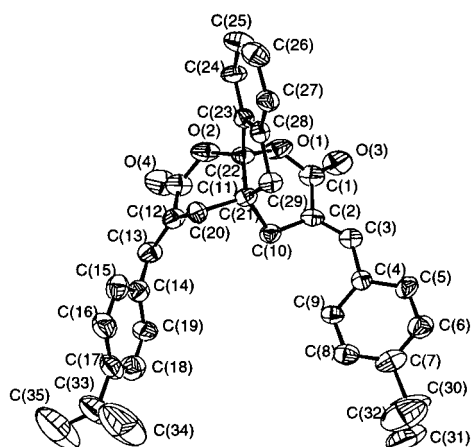
in the development of Baylis–Hillman chemistry as a source for useful organic transformation methodologies,<sup>6</sup> we have undertaken a research program on the application of Baylis–Hillman adducts for the synthesis of functionalized propellanes. Thus, we have envisaged that the bisalkylation at 2-position of 1-indanone with methyl 3-acetoxy-3-aryl-2-methylenepropanoates (acetates of the Baylis–Hillman adducts) followed by hydrolysis would lead to the formation of 2,2-bis[(2*E*)-2-carboxy-3-arylprop-2-en-1-yl]indan-1-ones. Subsequent lactonization under appropriate conditions might provide the desired propellano-bislactones (Scheme 1).

Accordingly, we have first selected methyl 3-acetoxy-3-phenylpropanoate (**1a**) as an alkylating agent for bisalkylation at the 2-position of 1-indanone. The best results were achieved when the bisalkylation of 1-indanone (**2**) (2 mM) was carried out with methyl 3-acetoxy-2-methylene-3-phenylpropanoate (**1a**) (5 mM) in the presence of NaH (10 mM) (excess) in benzene as solvent at reflux, thus providing the desired biscinnamic ester (**3a**) in 75% yield with high (*E*)-stereoselectivity after column chromatography (silica gel, 15% EtOAc in hexanes).<sup>7</sup> This compound is contaminated with (*Z*)-isomer (~12%) and other unidentified impurities

**Table 1.** Synthesis of Propellano-bislactones ( $1^a \rightarrow 3^b \rightarrow 4^c \rightarrow 5$ ) and ( $1^a \rightarrow 7^b \rightarrow 8^c \rightarrow 9^a$ )

allyl acetate	Ar	<b>2</b> ( $n = 1$ )/ <b>6</b> ( $n = 2$ )	product <sup>d</sup> <b>3, 7a</b>	yield <sup>e</sup> (%)	product <sup>f</sup> <b>4, 8a</b>	yield <sup>g</sup> (%)	product <sup>h</sup> <b>5, 9a</b>	yield <sup>i</sup> (%)
<b>1a</b>	phenyl	<b>2</b>	<b>3a</b>	75	<b>4a</b>	71	<b>5a</b> <sup>j</sup>	92
<b>1b</b>	4-methylphenyl	<b>2</b>	<b>3b</b>	74	<b>4b</b>	70	<b>5b</b> <sup>j</sup>	91
<b>1c</b>	4-ethylphenyl	<b>2</b>	<b>3c</b>	70	<b>4c</b>	75	<b>5c</b> <sup>j</sup>	84
<b>1d</b>	4-isopropylphenyl	<b>2</b>	<b>3d</b>	77	<b>4d</b>	72	<b>5d</b> <sup>j,k</sup>	89
<b>1e</b>	2-chlorophenyl	<b>2</b>	<b>3e</b>	74	<b>4e</b>	70	<b>5e</b> <sup>j</sup>	86
<b>1f</b>	4-chlorophenyl	<b>2</b>	<b>3f</b>	66	<b>4f</b>	73	<b>5f</b> <sup>j</sup>	90
<b>1g</b>	4-methoxyphenyl	<b>2</b>	<b>3g</b>	81	<b>4g</b>	72	<b>5g</b> <sup>j</sup>	85
<b>1a</b>	phenyl	<b>6</b>	<b>7a</b>	59	<b>8a</b>	81 <sup>l</sup>	<b>9a</b> <sup>k</sup>	68

<sup>a</sup> All the reactions were carried out on 2 mM scale of 1-indanone (**2**) [or 1-tetralone (**6**)] with 5 mM of the allyl acetate in the presence of excess NaH (10 mM) in benzene at reflux for 30 h in N<sub>2</sub> atm. <sup>b</sup> Hydrolysis was carried out on 1 mM scale of biscinnamic ester (**3a–g**, **7a**) with KOH/MeOH (1 g in 4 mL) at room temperature for 3 h. <sup>c</sup> Bis-lactonization was carried out on 0.5 mM scale of biscinnamic acid (**4a–g**, **8a**) with TFAA (1 mM) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at room temperature for 1.5 h in N<sub>2</sub> atm. <sup>d</sup> All of the biscinnamic esters were obtained as colorless viscous liquids. <sup>e</sup> <sup>1</sup>H (200 MHz) and <sup>13</sup>C (50 MHz) NMR spectral data of compounds **3a–g** indicate the presence of *Z*-isomer (ca. 5–15%) (in the case of **7a** there is ~18% *Z*-isomer) and also some unidentified impurities (ca. 5–7%). <sup>f</sup> Yields of the biscinnamates (with impurities as mentioned in the above footnote) after column chromatography (silica gel, 15% ethyl acetate in hexanes). <sup>g</sup> The compounds **4a–g** were obtained as colorless solids with 100% (*E*)-stereochemistry and gave satisfactory IR and <sup>1</sup>H (200 MHz) and <sup>13</sup>C (50 MHz) NMR spectral data. The compound **8a** was obtained as mixture of (*E*)- and (*Z*)-isomers in the ratio of ca. 85:15 and also contains some unidentified impurities (~5%). <sup>h</sup> Yields of the pure biscinnamic acids after crystallization from mixtures of EtOAc and hexanes. <sup>i</sup> All of the bislactones were obtained as colorless crystalline solids and gave satisfactory IR and <sup>1</sup>H (200 MHz) and <sup>13</sup>C (50 MHz) NMR spectral data and elemental analyses. <sup>j</sup> Yields of the pure bislactones after crystallization from mixtures of EtOAc and hexanes. <sup>k</sup> Compounds **5a–e** and **5g** were also characterized by mass spectral data. <sup>l</sup> Structures of the compounds **5d** and **9a** were further confirmed by single-crystal X-ray data (Figures 1 and 2). <sup>l</sup> Yield of the biscinnamic acid (**8a**) (*E*- & *Z*-isomers and with impurities as mentioned in the above footnote f).



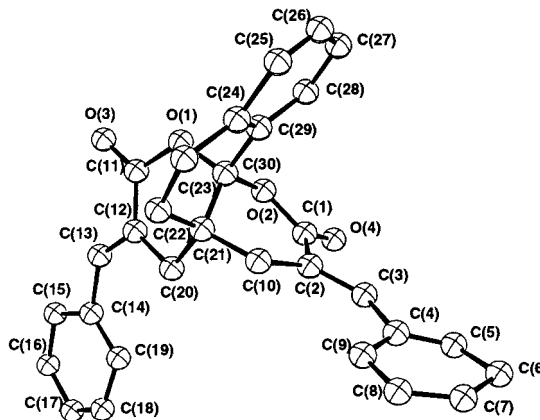
**Figure 1.** ORTEP diagram of compound **5d**.

(~5%). However, subsequent hydrolysis of this biscinnamic ester (**3a**) as such, with KOH/MeOH followed by crystallization from a mixture of EtOAc and hexanes (1:2), furnished the desired biscinnamic acid (**4a**) with exclusive (*E*)-stereochemistry in 71% yield.<sup>7</sup> Bislactonization of this biscinnamic acid (**4a**) was accomplished via treatment with trifluoroacetic anhydride (TFAA) in CH<sub>2</sub>Cl<sub>2</sub> at room temperature for 1.5 h to provide the desired 11,16-di[(*E*)-benzylidene]-13,14-dioxatetracyclo[7.4.4.0.1.9.0<sup>2,7</sup>]heptadeca-2,4,6-triene-12,15-dione (**5a**) in 92% yield as a crystalline solid.<sup>7,8</sup> This result is indeed very encouraging. We then successfully transformed a representative class of acetates

(7) **Typical Experimental Procedure (3a, 4a, 5a).** (a) 2,2-Bis[(*E*)-2-methoxycarbonyl-3-phenylprop-2-en-1-yl]indan-1-one (**3a**). To oil-free NaH (10 mM, 0.24 g) in dry benzene (15 mL) were added 1-indanone (2 mM, 0.264 g) and methyl 3-acetoxy-3-phenyl-2-methylenepropanoate (5 mM, 1.17 g) at room temperature, and the mixture was heated at 80 °C for 30 h under N<sub>2</sub> atmosphere with stirring. Then reaction mixture was allowed to come to room temperature and cooled to 0 °C. Excess NaH was destroyed by very slow and careful addition of acetic acid (1 mL). The reaction mixture was diluted with water (15 mL) and extracted with ether (3 × 20 mL). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was evaporated, and the crude product thus obtained was purified by column chromatography (15% ethyl acetate in hexanes) to provide 0.72 g (75%) of **3a** as viscous liquid. This compound is contaminated with (*Z*)-isomer (~12%) and other unidentified impurities (~5%). However, this was used as such for hydrolysis as described in the following. (b) 2,2-Bis[(*E*)-2-carboxy-3-phenylprop-2-en-1-yl]indan-1-one (**4a**). To a stirred solution of 2,2-bis[(*E*)-2-methoxycarbonyl-3-phenylprop-2-en-1-yl]indan-1-one (**3a** obtained as above) (1 mM, 0.48 g) in MeOH (2 mL) was added a solution of KOH (85% KOH pellets, 1 g) in MeOH (4 mL). After the mixture stirred for 3 h at room temperature, MeOH was removed. Then the reaction mixture was diluted with water (15 mL) and washed with ether (2 × 20 mL) to remove any organic impurities. The aqueous layer was acidified with 2 N HCl solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude product thus obtained was purified by crystallization [ethyl acetate/hexanes (1:2)] to provide biscinnamic acid (**4a**) as a crystalline solid (0.32 g, 71%) with exclusive (*E*)-stereochemistry. (c) 11,16-Di[(*E*)-benzylidene]-13,14-dioxatetracyclo[7.4.4.0.1.9.0<sup>2,7</sup>]heptadeca-2,4,6-triene-12,15-dione (**5a**). To a stirred solution of 2,2-bis[(*E*)-2-carboxy-3-phenylprop-2-en-1-yl]indan-1-one (**4a** obtained as above) (0.5 mM, 0.226 g) in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added trifluoroacetic anhydride (TFAA) (1 mM, 0.21 g). After stirring for 1.5 h at room temperature under N<sub>2</sub> atmosphere, the reaction mixture was diluted with water (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The combined organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was evaporated, and the crude solid thus obtained was purified by crystallization [ethyl acetate/hexanes (2:3)] to provide 0.20 g (92%) of propellano-bis lactone (**5a**) as a crystalline solid.

of the Baylis–Hillman adducts (**1a–g**) into various propellano-bis lactones (**5a–g, 9a**) (Scheme 1, Table 1).

To ensure the formation of propellano-bis lactones we obtained single crystals in the case of **5d** and **9a** and established the structures by X-ray crystallography data (Figures 1 and 2).<sup>9</sup>



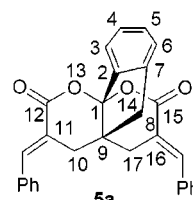
**Figure 2.** ORTEP diagram of compound **9a**.

In conclusion, we have developed a simple and convenient methodology for the preparation of functionalized dioxo-

(8) **Spectral data for the compound 5a:** mp = 200–201 °C; IR (KBr) 1740, 1623 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz) (CDCl<sub>3</sub>) δ 2.75 (dd, 2H, *J* = 1.8 Hz, and 15.8 Hz),<sup>10</sup> 2.95 (d, *J* = 1.8 Hz) & 3.02 (s) [4H],<sup>10</sup> 7.15–7.49 (m, 13H), 7.69–7.80 (m, 1H), 7.89 (s, 2H); <sup>13</sup>C NMR (50 MHz) (CDCl<sub>3</sub>) δ 33.22, 42.55, 43.14, 111.88, 122.75, 124.28, 125.50, 128.25, 128.76, 129.54, 129.83, 131.02, 134.22, 139.29, 139.64, 143.86, 164.07; MS (*m/z*) 434 (M<sup>+</sup>). Anal. Calcd for C<sub>29</sub>H<sub>22</sub>O<sub>4</sub>: C, 80.17; H, 5.10. Found: C, 80.11; H, 5.14.

(9) Detailed X-ray crystallographic data for the compound **5d** and **9a** are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K. (For **5d**, CCDC no. 151753, and for **9a**, CCDC no. 155409). Crystal data for C<sub>35</sub>H<sub>34</sub>O<sub>4</sub> (**5d**): *M* = 518.62, colorless crystal, crystal dimensions 0.7 × 0.6 × 0.6 mm<sup>3</sup>, monoclinic, space group *P*2<sub>1</sub>/*n* (No. 14), *a* = 16.377(2) Å, *b* = 10.404(3) Å, *c* = 16.595(2) Å, β = 94.106° (11), *V* = 2820.4(9) Å<sup>3</sup>, *Z* = 4, ρ<sub>calcd</sub> = 1.221 g cm<sup>-3</sup>, μ = 0.079 mm<sup>-1</sup>, F(000) = 1104, index ranges 0 ≤ *h* ≤ 19, 0 ≤ *k* ≤ 12, -19 ≤ *l* ≤ 19. θ range, 1.69–24.98°; 356 variables and 0 restraints were refined for 2048 independent reflections with *I* ≥ 2σ(*I*) to R = 0.0581, wR<sup>2</sup> = 0.1345, GOF = 1.044. Crystal data for C<sub>30</sub>H<sub>24</sub>O<sub>4</sub> (**9a**): *M* = 448.49, colorless crystal, crystal dimensions 0.96 × 0.36 × 0.28 mm<sup>3</sup>, monoclinic, space group *P*2<sub>1</sub>/*c* (No. 14), *a* = 8.9137(10) Å, *b* = 11.806(4) Å, *c* = 21.405(3) Å, β = 93.556° (10), *V* = 2248.3(8) Å<sup>3</sup>, ρ<sub>calcd</sub> = 1.325 g cm<sup>-3</sup>, μ = 0.087 mm<sup>-1</sup>, F(000) = 944, index ranges from 0 ≤ *h* ≤ 10, 0 ≤ *k* ≤ 14, -25 ≤ *l* ≤ 25. θ range 1.91–24.97°; 308 variables and 0 restraints were refined for 1876 independent reflections with *I* ≥ 2σ(*I*) to R = 0.0528, wR<sup>2</sup> = 0.1324, GOF = 1.090

(10) It looks that both the allylic CH<sub>2</sub> protons (four protons) (at C-10 and C-17) appear as AB part of ABX system (doublet of AB quartet, i.e., two dd) and the downfield doublet (of this system) is merged with singlet at δ 3.02 of benzylic CH<sub>2</sub> protons (at C-8). This is confirmed by the very clear appearance of AB quartet for both the allylic CH<sub>2</sub> protons (four protons) (at C-10 and C-17) when the <sup>1</sup>H NMR spectrum was recorded in the presence of the shift reagent Eu(fod)<sub>3</sub>.



propellanes using acetates of the Baylis–Hillman adducts, thus demonstrating the efficacy of Baylis–Hillman chemistry in synthetic organic chemistry.

**Acknowledgment.** We thank DST (New Delhi) for funding this project. We thank the UGC (New Delhi) for Special Assistance Program in organic chemistry in the School of Chemistry, University of Hyderabad. T.S.N. thanks UGC (New Delhi) for his research fellowship. We thank the National Single Crystal X-ray facility, School of Chemistry,

University of Hyderabad, funded by DST (New Delhi). We thank Dr. T. P. Radhakrishnan for helpful discussions regarding X-ray crystal structure.

**Supporting Information Available:** Melting points, IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral data, and  $^{13}\text{C}$  NMR spectra of all propellano-bislactones (**5a–g**, **9a**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL016469W