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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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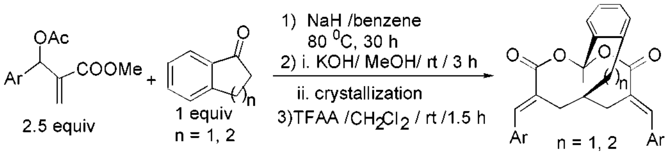
ABSTRACT



A simple and convenient synthesis of 11,16-di[(*E*)-arylidene]-13,14-dioxatetracyclo-[7.4.4.0.^{1,9}0^{2,7}]heptadeca-2,4,6-triene-12,15-diones and 12,-17-di[(*E*)-benzylidene]-14,15-dioxatetracyclo[8.4.4.0.^{1,10}0^{2,7}]octadeca-2,4,6-triene-13,16-dione, i.e., 2,10-dioxa[4.4.3]propellane-3,9-diones and 2,-10-dioxa[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.[1] The polycyclic polylactone framework is an important structural feature present in various biologically active and natural products.[2] 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[3] using acetates of the Baylis−Hillman adducts.

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.[4−6] In continuation of our interest

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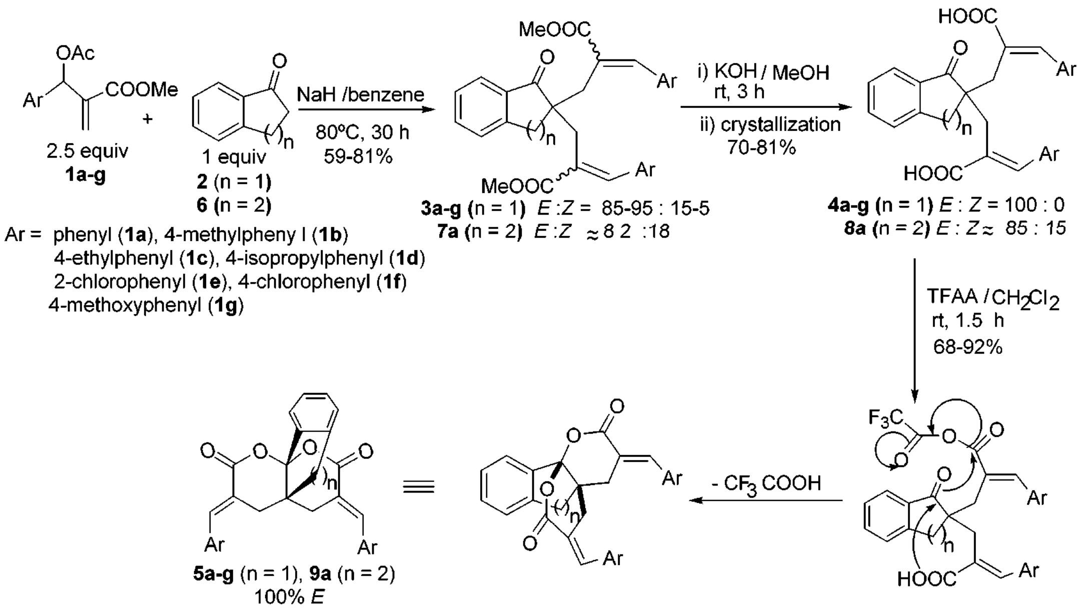
Scheme 1



in the development of Baylis–Hillman chemistry as a source for useful organic transformation methodologies,[6] 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).[7] This compound is contaminated with (*Z*)-isomer (~12%) and other unidentified impurities

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

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

[a] 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_2 atm. [b] 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. [c] Bislactonization was carried out on 0.5 mM scale of biscinnamic acid (**4a**–**g**, **8a**) with TFAA (1 mM) in CH_2Cl_2 (5 mL) at room temperature for 1.5 h in N_2 atm. [d] All of the biscinnamic esters were obtained as colorless viscous liquids. ^1H (200 MHz) and ^{13}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%). [e] Yields of the biscinnamates (with impurities as mentioned in the above footnote) after column chromatography (silica gel, 15% ethyl acetate in hexanes). [f] The compounds **4a**–**g** were obtained as colorless solids with 100% (*E*)-stereochemistry and gave satisfactory IR and ^1H (200 MHz) and ^{13}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%). [g] Yields of the pure biscinnamic acids after crystallization from mixtures of EtOAc and hexanes. [h] All of the bislactones were obtained as colorless crystalline solids and gave satisfactory IR and ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectral data and elemental analyses. [i] Yields of the pure bislactones after crystallization from mixtures of EtOAc and hexanes. [j] Compounds **5a**–**e** and **5g** were also characterized by mass spectral data. [k] Structures of the compounds **5d** and **9a** were further confirmed by single-crystal X-ray data (Figures 1 and 2). [l] Yield of the biscinnamic acid (**8a**) (*E*- & *Z*-isomers and with impurities as mentioned in the above footnote f).

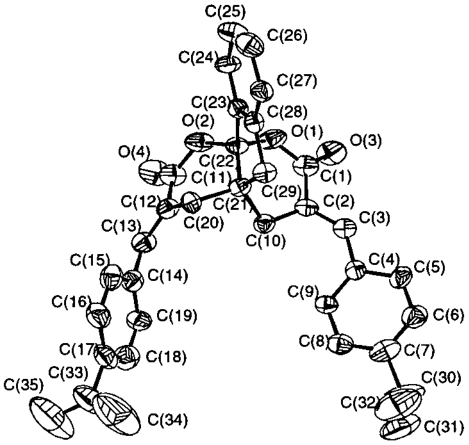


Figure 1. ORTEP diagram of compound **5d**.

(~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.[7] Bislactonization of this biscinnamic acid (**4a**) was accomplished via treatment with triflouroacetic anhydride (TFAA) in CH_2Cl_2 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^{2,7}]heptadeca-2,4,6-triene-12,15-dione (**5a**) in 92% yield as a crystalline solid.[7,8] This result is indeed very encouraging. We then successfully transformed a representative class of acetates of the Baylis–Hillman adducts (**1a–g**) into various propellano-bislactones (**5a–g**, **9a**) (Scheme 1, Table 1).

To ensure the formation of propellano-bislactones we obtained single crystals in the case of **5d** and **9a** and established the structures by X-ray crystallography data (Figures 1 and 2).[9]

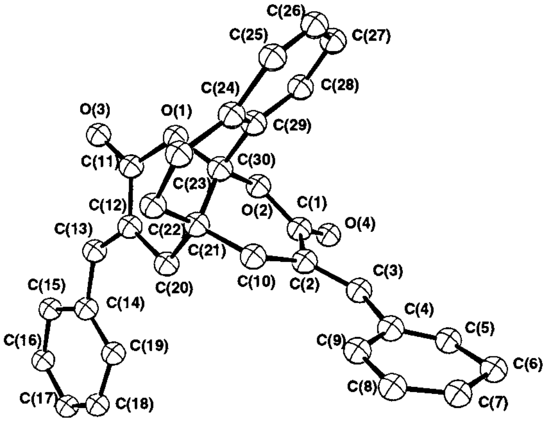


Figure 2. ORTEP diagram of compound **9a**.

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

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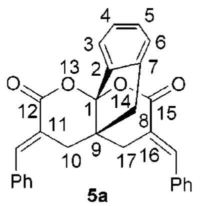
(7) **Typical Experimental Procedure (3a, 4a, 5a).** (a) 2,2-Bis[(2*E*)-2-methoxycarbonyl-3-phenylprop-2-en-1-yl]indan-1-one (**3a**). To oil-free NaH (10 mM, 0.24 g) in dry benzene (15 mL) were added 1-indanone (2 mM, 0.264 g) and methyl 3-acetoxy-3-phenyl-2-methylenepropanoate (5 mM, 1.17 g) at room temperature, and the mixture was heated at 80 °C for 30 h under N_2 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_2SO_4. 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[(2*E*)-2-carboxy-3-phenylprop-2-en-1-yl]indan-1-one (**4a**). To a stirred solution of 2,2-bis[(2*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_2SO_4 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^{2,7}]heptadeca-2,4,6-triene-12,15-dione (**5a**). To a stirred solution of 2,2-bis[(2*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_2Cl_2 (5 mL) was added triflouroacetic anhydride (TFAA) (1 mM, 0.21 g). After stirring for 1.5 h at room temperature under N_2 atmosphere, the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4. 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-bislactone (**5a**) as a crystalline solid.

(8) **Spectral data for the compound 5a:** mp = 200–201 °C; IR (KBr) 1740, 1623 cm^{-1}; ^{1}H NMR (200 MHz) ($CDCl_3$) δ 2.75 (dd, 2H, J = 1.8 Hz, and 15.8 Hz),[10] 2.95 (d, J = 1.8 Hz) & 3.02 (s) [4H],[10] 7.15–7.49 (m, 13H), 7.69–7.80 (m, 1H), 7.89 (s, 2H); ^{13}C NMR (50 MHz) ($CDCl_3$) 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^+). Anal. Calcd for $C_{29}H_{22}O_4$: 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 $C_{35}H_{34}O_4$ (**5d**): M = 518.62, colorless crystal, crystal dimensions 0.7 × 0.6 × 0.6 mm^3, monoclinic, space group $P2_1/n$ (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^3, Z = 4, ρ_{calcd} = 1.221 g cm^{-3}, μ = 0.079 mm^{-1}, F(000) = 1104, index ranges $0 \leq h \leq 19$, $0 \leq k \leq 12$, $-19 \leq l \leq 19$. θ range, 1.69–24.98°; 356 variables and 0 restraints were refined for 2048 independent reflections with $I \geq 2\sigma(I)$ to R = 0.0581, wR^2 = 0.1345, GOF = 1.044. Crystal data for $C_{30}H_{24}O_4$ (**9a**): M = 448.49, colorless crystal, crystal dimensions 0.96 × 0.36 × 0.28 mm^3, monoclinic, space group $P2_1/c$ (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^3, ρ_{calcd} = 1.325 g cm^{-3}, μ = 0.087 mm^{-1}, F(000) = 944, index ranges from $0 \leq h \leq 10$, $0 \leq k \leq 14$, $-25 \leq l \leq 25$. θ range 1.91–24.97°; 308 variables and 0 restraints were refined for 1876 independent reflections with $I \geq 2\sigma(I)$ to R = 0.0528, wR^2 = 0.1324, GOF = 1.090

(10) It looks that both the allylic CH_2 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_2 protons (at C-8). This is confirmed by the very clear appearance of AB quartet for both the allylic CH_2 protons (four protons) (at C-10 and C-17) when the ^{1}H NMR spectrum was recorded in the presence of the shift reagent Eu(fod)$_3$.



5a

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

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Supporting Information Available: Melting points, IR, ^{1}H and ^{13}C NMR spectral data, and ^{13}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.

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