Tetrahedron 64 (2008) 10267–10271

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of highly substituted *m*-chlorophenolic biaryls by chlorine substituent-promoted Diels–Alder reaction of 2-aryl-3-chlorofurans

Ram N. Ram *, Neeraj Kumar

Department of Chemistry, Indian Institute of Technology, Delhi, Hauz Khas, New Delhi 110016, India

ARTICLE INFO

Article history:
Received 17 May 2008
Received in revised form 14 July 2008
Accepted 15 July 2008
Available online 18 July 2008

Keywords:
3-Chlorofurans
Diels–Alder reaction
Dimethyl acetylenedicarboxylate
Chlorophenolic biaryls
Chlorine effect

ABSTRACT

Chlorine substituent-promoted Diels–Alder reaction of 2-aryl-3-chlorofurans with dimethyl acetylenedicarboxylate at 100 °C afforded highly substituted *m*-chlorophenolic biaryls in 59–78% yields.

© 2008 Published by Elsevier Ltd.

1. Introduction

Biaryl structural unit is present in several bioactive natural products,[1] pharmaceuticals,[2] ligands of organometallic catalysts,[3] optoelectronics materials[4] and supramolecular assemblies.[5] A large number of biaryls in these applications are phenolic biaryls. Several modern methods for the preparation of biaryls are available, which involve transition metal-catalyzed cross-coupling of aryl halides (or less frequently pseudo-halides) with an aryl organometallic.[6] Phenolic biaryls may be prepared by these methods directly from iodophenols. However, the less reactive but more easily accessible chloro or bromophenols may be problematic unless the phenolic group is protected in an additional step because the halogen atom is deactivated further by the hydroxylate donor group formed under the basic conditions employed.[7] Therefore, direct biaryl coupling of phenols have generally been realized by their oxidative coupling,[6g,8] which is believed to be the Nature's way of biaryl synthesis,[9] although some satisfactory Suzuki coupling procedures with bromophenols[7,10] and a few methods involving direct arylation of phenols with aryl halides[11] have recently been reported. An alternative approach to phenolic biaryls involving Diels–Alder reaction of 1-aryl-3-siloxybuta-1,3-dienes with acetylenic dienophiles followed by aromatization of the cycloadduct with DDQ has also been reported.[12] This approach to general biaryl synthesis has received renewed interest in recent times because it has the advantage of atom economy, does not generate waste stream and would not be complicated by regiochemical problem in the synthesis of biaryls containing a nucleofugal group, such as bromo or iodo.[13] Diels–Alder reaction of furans with acetylenic dienophiles would furnish phenolic biaryls either directly or by acid-catalyzed ring-opening of the intermediate oxabicycloheptadiene adduct.[14] However, there are only a few reports on the synthesis of phenolic biaryls through Diels–Alder reaction of 2-aryl furans, which afforded some simple phenolic biaryls in low to moderate yields along with oxabicyloheptadiene adducts in many cases and required long reaction time and/or Lewis acid catalysis.[15] This is probably because the efficiency of furan Diels–Alder reaction is generally afflicted by the low reactivity of a furano diene due to its aromaticity and reversibility of the reaction due to the formation of strained oxabicyclo adduct. Therefore, the need to improve this synthetically versatile reaction[16] cannot be over-emphasized. Therefore, several improved procedures that involve catalysis by Lewis acids[17] have been developed. High pressure,[18] microwave heating[19] and ultrasound[20] have also been reported to have beneficial effects on the reaction. An alternative strategy in this respect is to use a halofuran. Experimental results show that a halogen substituent on furan ring enhances the rate and efficiency of furan Diels–Alder reaction and decreases its reversibility.[21] This, the so-called 'halogen effect' has recently been validated by theoretical calculations also.[22] An added advantage of this approach is that the halogen functionality in the adduct can be elaborated further or easily removed.

Recently, we reported the synthesis of some 2-aryl-3-chlorofurans by using CuCl/bpy-catalyzed halogen atom transfer radical

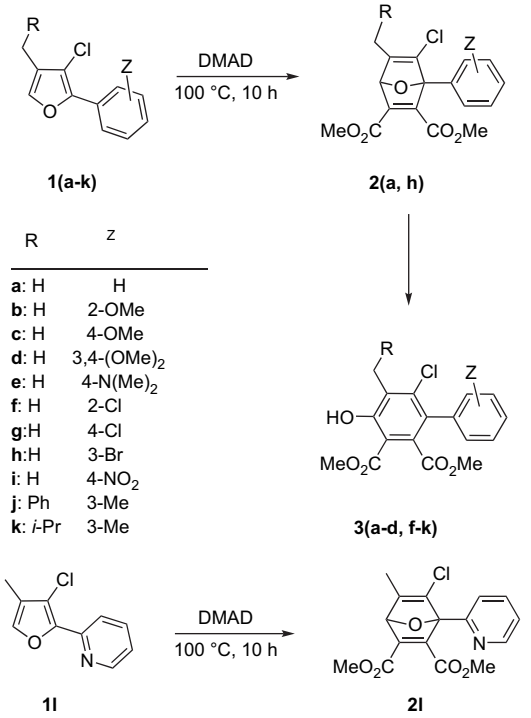
* Corresponding author. Tel.: +91 11 26591508; fax: +91 11 26582037.
E-mail address: rnram@chemistry.iitd.ernet.in (R.N. Ram).

0040-4020/$ – see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tet.2008.07.050

cyclization of 2,2,2-trichloroethyl allylic ethers as the key step.[23] Our results on Diels–Alder reaction of a few of these furans with dimethyl acetylenedicarboxylate (DMAD) provided an experimental support to the preponderance of 'halogen effect' on furan Diels–Alder reaction through an intramolecular competition between a 3-halofurano diene and a non-halogenated furano diene or a non-furano halodiene. We now wish to report the application of the chlorine substituent-promoted Diels–Alder reaction of these furans in the synthesis of hitherto unknown highly substituted *m*-chlorophenolic biaryls.

2. Result and discussion

Accordingly, the Diels–Alder reaction of the 2-aryl-3-chlorofurans **1** (Scheme 1) was performed by heating the chlorofurans with DMAD at 100 °C for 10 h under a reduced pressure of nitrogen atmosphere. The corresponding *m*-chlorophenolic biaryls **3**(**a**–**d**, **f**–**k**) were obtained directly in good yields in most of the cases (Table 1). Probably the chlorine substituent allowed the reaction to be performed at higher temperatures with little probability of reversal than normally used (room temperature), at which the initially formed oxabicycloheptadiene intermediates **2** opened thermally to the biaryls **3**. It is noteworthy that the nitro substituted furan **1i** (S.No. 8) afforded only the biaryl **3i** as against the reported reaction of 2-(4-nitrophenyl)furan with DMAD in which case the corresponding oxabicyclo adduct was isolated exclusively.[15b] The cycloadduct oxabicycloheptadiene **2** was isolated only in a few cases, such as **2a** and **2h**, which could be easily opened to the corresponding biaryls by treatment with $BF_3{\cdot}Et_2O$ at 60 °C for 2 h. However, the basic oxabicyclic adduct **2l** was refractory under these conditions. The Diels–Alder reaction of the basic chlorofuran **1e** gave a complex mixture of products, which deteriorated further to unidentified products on attempted purification by column chromatography. The reaction with some other acetylenic and ethylenic dienophiles, such as diphenylacetylene, *N*-phenylmaleimide and trichloroethylene failed. All the products have been well characterized by IR, ^1H and ^{13}C NMR spectroscopy and HRMS.



Scheme 1. Diels–Alder reaction of 2-aryl-3-chlorofurans **1**.

Table 1
Diels–Alder synthesis of biaryls **3**[a]

S.No.	Furan **1**	Z	R	Adduct **2**	Biaryl **3**
1	**a**	H	H	28	52 (76)[b]
2	**b**	2-OMe	H		62
3	**c**	4-OMe	H		68
4	**d**	3,4-$(OMe)_2$	H		78
5	**f**	2-Cl	H		59
6	**g**	4-Cl	H		65
7	**h**	3-Br	H	41	34 (67)[b]
8	**i**	4-NO_2	H		64
9	**j**	3-Me	Ph		73
10	**k**	3-Me	*i*-Pr		66

[a] All the reactions were perfomed in a closed vessel in the absence of a solvent under reduced pressure of a nitrogen atmosphere.
[b] Total isolated yield after opening of the oxabicyclo adduct **2** with $BF_3{\cdot}OEt_2$ at 60 °C for 2 h.

Curiously, the reaction did not proceed in refluxing toluene and occurred without a solvent, which was a welcomed value-addition to this approach from the environmental viewpoint. The reaction occurred at neutral pH and did not require a catalyst, which is generally unstable in air or expensive in the transition metal-catalyzed cross-coupling reactions. The bromobiaryl **3h** (Table 1, S.No. 7) could be synthesized regiospecifically without any problem of regiochemistry, which might arise in the biaryl coupling methods. Sterically hindered tri-*ortho*-substituted biaryls **3b** and **3f** could be obtained in acceptable yields. Besides the 'halogen effect,' the present reaction also distinguishes itself from the reported ones[15] by forming a fully substituted benzene ring. The newly formed benzene ring has an array of functional groups, which is otherwise difficult to assemble, such as OH and Cl *meta* to each other.[24] Since chlorine can act as hydrogen bond acceptor, it has been frequently used as a substitute of hydroxy group for bioactivity modulation in medicinal chemistry. The present method may be useful for the synthesis of analogs of bioactive resorcinolic biaryls[8a,25] to study structure–activity relationships.

3. Conclusions

In conclusion, the present work describes an improved atom economic furan Diels–Alder approach to the synthesis of highly substituted *m*-chlorophenolic biaryls under catalyst and solvent free environmentally benign reaction conditions.

4. Experimental

4.1. General remarks

IR spectra were recorded on Nicolet Protégé 460 ES-P FTIR spectrophotometer of the solid samples as KBr pellet and of the liquid samples as neat liquid film placed between KBr disks. NMR spectra were recorded on Bruker Spectrospin DPX 300 MHz FT NMR spectrometer in $CDCl_3$ with TMS as internal standard. High resolution mass spectra were recorded on a QSTAR XL, hybrid quadrupole-TOF LC/MS mass spectrometer of the institute using the electron spray ionization (ESI) in positive ion mode. Melting points were determined in an electrically heated apparatus by taking the sample in a glass capillary sealed at one end and are uncorrected. The progress of the reaction was monitored by TLC using a glass plate coated with a TLC grade silica gel. Iodine was used for visualizing the spots. Solvents were evaporated on a rotary evaporator under reduced pressure using an aspirator. The products were separated and purified by column chromatography using

silica gel (60–120 mesh) as the solid support. *n*-Hexane and its mixtures with ethyl acetate in variable proportions were used as the solvent for elution. R_f values were determined by performing thin layer chromatography on Merck DC-Alufolien silica gel $60WF_{254s}$ thin aluminium precoated plates using 20% EtOAc in *n*-hexane as the developing solvent.

4.2. Diels–Alder reaction of 3-chlrofurans 1: synthesis of *m*-chlorophenolic biaryls 3 and oxabicycloheptadiene adducts 2

General procedure: 3-Chlorofuran **1** (2 mmol) and DMAD (0.28 g, 2 mmol) were taken in a round bottom flask fitted with a two-way stopcock adapter. The flask was evacuated and filled with nitrogen and again evacuated. The flask was then placed in an oil bath maintained at 100 °C for 10 h. The flask was then cooled and the crude product was subjected to column chromatography (silica gel, *n*-hexane/ethyl acetate, 9:1 v/v) to give the *m*-chlorophenolic biaryls **3**. In the case of **1a** and **1h** where the oxabicycloheptadienes adducts **2a** and **2h**, respectively, were also formed, the latter were obtained by further elution of the column with the same solvent.

*4.2.1. Dimethyl 6-chloro-4-hydroxy-5-methylbiphenyl-2,3-dicarboxylate (**3a**)*

White solid; mp 118 °C (*n*-hexane/ether); R_f (20% EtOAc/*n*-hexane) 0.60; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.54 (s, D_2O-exchangeable, 1H, ArOH), 7.38–7.19 (m, 5H, ArH), 3.90 (s, 3H, $COOCH_3$), 3.44 (s, 3H, $COOCH_3$), 2.40 (s, 3H, $ArCH_3$) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.6 (C), 167.9 (C), 159.7 (C), 141.1 (C), 136.6 (C), 133.7 (C), 130.1 (2×CH), 128.0 (CH), 127.8 (2×CH), 127.1 (C), 106.6 (C), 53.1 (CH_3), 52.0 (CH_3), 13.4 (CH_3) ppm; IR (KBr): ν_{max} 3458 (br), 1741, 1664, 1346, 1234 cm^{-1}; HRMS (ESI): $[M+Na]^+$, found 357.0505. $C_{17}H_{15}ClO_5Na$ requires 357.0506.

*4.2.2. Dimethyl 6-chloro-5-methyl-1-phenyl-7-oxabicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**2a**)*

White solid; mp 110 °C (*n*-hexane/ether); R_f (20% EtOAc/*n*-hexane) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57–7.43 (m, 5H, ArH), 5.65 (s, 1H, bridge-head H), 3.83 (s, 3H, $COOCH_3$), 3.78 (s, 3H, $COOCH_3$), 2.0 (s, 3H, $=CCH_3$) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.2 (C), 162.3 (C), 158.5 (C), 148.1 (C), 146.7 (C), 143.0 (C), 131.6 (C), 129.0 (CH), 128.3 (2×CH), 126.8 (2×CH), 98.3 (C), 85.8 (CH), 52.52 (CH_3), 52.48 (CH_3), 12.3 (CH_3) ppm; IR (KBr): ν_{max} 1728, 1648, 1438, 1347, 1272, 738 cm^{-1}; HRMS (ESI): $[2M+Na]^+$, found 691.1110. $C_{34}H_{30}Cl_2O_{10}Na$ requires 691.1114.

*4.2.3. Dimethyl 6-chloro-4-hydroxy-2′-methoxy-5-methylbiphenyl-2,3-dicarboxylate (**3b**)*

White solid; mp 114 °C (*n*-hexane/ether); R_f (20% EtOAc/*n*-hexane) 0.45; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.56 (s, D_2O-exchangeable, 1H, ArOH), 7.39–6.92 (m, 4H, ArH), 3.88 (s, 3H, $ArOCH_3$), 3.76 (s, 3H, $COOCH_3$), 3.45 (s, 3H, $COOCH_3$), 2.39 (s, 3H, $ArCH_3$) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.6 (C), 167.9 (C), 159.8 (C), 157.6 (C), 141.9 (C), 133.7 (C), 131.7 (CH), 129.9 (CH), 127.1 (C), 126.8 (C), 125.6 (C), 120.0 (CH), 110.8 (CH), 106.7 (C), 55.8 (CH_3), 52.9 (CH_3), 51.9 (CH_3), 13.3 (CH_3) ppm; IR (KBr): ν_{max} 3452 (br), 1739, 1678, 1226, 752 cm^{-1}; HRMS (ESI): $[M+Na]^+$, found 387.0618. $C_{18}H_{17}ClO_6Na$ requires 387.0611.

*4.2.4. Dimethyl 6-chloro-4-hydroxy-4′-methoxy-5-methylbiphenyl-2,3-dicarboxylate (**3c**)*

White solid; mp 104 °C (*n*-hexane/ether); R_f (20% EtOAc/*n*-hexane) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.54 (s, D_2O-exchangeable, 1H, ArOH), 7.12 (d, J=9 Hz, 2H, ArH), 6.91 (d, J=9 Hz, 2H, ArH), 3.90 (s, 3H, $ArOCH_3$), 3.84 (s, 3H, $COOCH_3$), 3.49 (s, 3H, $COOCH_3$), 2.39 (s, 3H, $ArCH_3$) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.6 (C), 168.0 (C), 159.6 (C), 159.2 (C), 141.6 (C), 134.0 (C), 131.3 (2×CH), 129.9 (C), 128.8 (C), 127.0 (C), 113.3 (2×CH), 106.6 (C), 55.2 (CH_3), 53.1 (CH_3), 52.0 (CH_3), 13.4 (CH_3) ppm; IR (KBr): ν_{max} 3443 (br), 1738, 1668, 1236, 1034 cm^{-1}; HRMS (ESI): $[2M+Na]^+$, found 751.1324. $C_{36}H_{34}Cl_2O_{12}Na$ requires 751.1325.

*4.2.5. Dimethyl 6-chloro-4-hydroxy-3′,4′-dimethoxy-5-methylbiphenyl-2,3-dicarboxylate (**3d**)*

White solid; mp 121 °C (*n*-hexane/ether); R_f (20% EtOAc/*n*-hexane) 0.35; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.61 (s, D_2O-exchangeable, 1H, ArOH), 6.93 (d, J=9 Hz, 1H, ArH), 6.83–6.78 (m, 2H, ArH), 3.96 (s, 3H, $ArOCH_3$), 3.95 (s, 3H, $ArOCH_3$), 3.90 (s, 3H, $COOCH_3$), 3.56 (s, 3H, $COOCH_3$), 2.44 (s, 3H, $ArCH_3$) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.4 (C), 167.9 (C), 159.5 (C), 148.5 (C), 148.0 (C), 141.3 (C), 133.8 (C), 129.7 (C), 128.8 (C), 126.9 (C), 122.5 (CH), 113.4 (CH), 110.2 (CH), 106.4 (C), 55.7 (CH_3), 55.6 (CH_3), 53.0 (CH_3), 52.0 (CH_3), 13.3 (CH_3) ppm; IR (KBr): ν_{max} 3449 (br), 1738, 1669, 1451, 1233, 1040 cm^{-1}; HRMS (ESI): $[M+Na]^+$, found 417.0718. $C_{19}H_{19}ClO_7Na$ requires 417.0717.

*4.2.6. Dimethyl 2′,6-dichloro-4-hydroxy-5-methylbiphenyl-2,3-dicarboxylate (**3f**)*

White solid; mp 124 °C (*n*-hexane/ether); R_f (20% EtOAc/*n*-hexane) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.55 (s, D_2O-exchangeable, 1H, ArOH), 7.40–7.09 (m, 4H, ArH), 3.83 (s, 3H, $COOCH_3$), 3.39 (s, 3H, $COOCH_3$), 2.34 (s, 3H, $ArCH_3$) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.4 (C), 167.5 (C), 160.2 (C), 141.1 (C), 135.4 (C), 134.9 (C), 133.5 (C), 131.7 (CH), 129.7 (CH), 129.2 (CH), 127.5 (C), 127.1 (C), 126.3 (CH), 106.7 (C), 53.1 (CH_3), 52.0 (CH_3), 13.3 (CH_3) ppm; IR (KBr): ν_{max} 3459 (br), 1743, 1672, 1348, 1230, 756 cm^{-1}; HRMS (ESI): $[M+Na]^+$, found 391.0116. $C_{17}H_{14}Cl_2O_5Na$ requires 391.0116.

*4.2.7. Dimethyl 4′,6-dichloro-4-hydroxy-5-methylbiphenyl-2,3-dicarboxylate (**3g**)*

White solid; mp 106 °C (*n*-hexane/ether); R_f (20% EtOAc/*n*-hexane) 0.65; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.57 (s, D_2O-exchangeable, 1H, ArOH), 7.35 (d, J=9 Hz, 2H, ArH), 7.13 (d, J=9 Hz, 2H, ArH), 3.91 (s, 3H, $COOCH_3$), 3.50 (s, 3H, $COOCH_3$), 2.39 (s, 3H, $ArCH_3$) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.4 (C), 167.7 (C), 159.9 (C), 140.8 (C), 135.0 (C), 134.1 (C), 133.7 (C), 131.6 (2×CH), 128.8 (C), 128.1 (2×CH), 127.3 (C), 106.7 (C), 53.2 (CH_3), 52.1 (CH_3), 13.4 (CH_3) ppm; IR (KBr): ν_{max} 3440 (br), 1749, 1674, 1348, 1226, 756 cm^{-1}; HRMS (ESI): $[M+Na]^+$, found 391.0131. $C_{17}H_{14}Cl_2O_5Na$ requires 391.0116.

*4.2.8. Dimethyl 1-(3-bromophenyl)-6-chloro-5-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**2h**)*

White solid; mp 79 °C (*n*-hexane/ether); R_f (20% EtOAc/*n*-hexane) 0.60; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (t, J=3.0 Hz, 1H, ArH), 7.54 (td, J=7.8, 0.9 Hz, 1H, ArH), 7.49 (dd, J=7.8, 1.0 Hz, 1H, ArH), 7.31 (t, J=7.9 Hz, 1H, ArH), 5.63 (s, 1H, bridge-head H), 3.81 (s, 3H, $COOCH_3$), 3.78 (s, 3H, $COOCH_3$), 1.97 (s, 3H, $=CCH_3$) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.8 (C), 162.1 (C), 157.8 (C), 148.0 (C), 146.7 (C), 142.4 (C), 133.6 (C), 132.1 (CH), 129.79 (CH), 129.76 (CH), 125.3 (CH), 122.4 (C), 97.1 (C), 85.7 (CH), 52.58 (CH_3), 52.52 (CH_3), 12.2 (CH_3) ppm; IR (KBr): ν_{max} 1729, 1654, 1431, 1305, 1259, 1117 cm^{-1}; HRMS (ESI): $[M+Na]^+$, found 434.9610. $C_{17}H_{14}BrClO_5Na$ requires 434.9611.

*4.2.9. Dimethyl 3′-bromo-6-chloro-4-hydroxy-5-methylbiphenyl-2,3-dicarboxylate (**3h**)*

White solid; mp 102 °C (*n*-hexane/ether); R_f (20% EtOAc/*n*-hexane) 0.65; ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.52 (s, D_2O-exchangeable, 1H, ArOH), 7.44 (ddd, J=7.8, 1.8. 1.2 Hz, 1H, ArH), 7.31 (t, J=1.4 Hz, 1H, ArH), 7.19 (dt, J=7.8, 0.8 Hz, 1H, ArH), 7.08 (td, J=7.8, 1.2 Hz, 1H, ArH), 3.84 (s, 3H, $COOCH_3$), 3.45 (s, 3H, $COOCH_3$), 2.32 (s,

3H, $ArCH_3$) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.4 (C), 167.6 (C), 159.9 (C), 140.6 (C), 138.4 (C), 133.7 (C), 133.1 (CH), 131.1 (CH), 129.3 (CH), 128.9 (CH), 128.5 (C), 127.3 (C), 121.7 (C), 106.7 (C), 53.1 (CH_3), 52.1 (CH_3), 13.3 (CH_3) ppm; IR (KBr): ν_{max} 3075 (br), 1749, 1673, 1346, 1219 cm^{-1}; HRMS (ESI): $[M+Na]^+$, found 434.9611. $C_{17}H_{14}BrClO_5Na$ requires 434.9611.

4.2.10. Dimethyl 6-chloro-4-hydroxy-5-methyl-4′-nitrobiphenyl-2,3-dicarboxylate (**3i**)

Yellow solid; mp 127 °C (*n*-hexane/ether); R_f (20% EtOAc/*n*-hexane) 0.40; ^1H NMR (300 MHz, $CDCl_3$): δ 11.63 (s, D_2O-exchangeable, 1H, ArOH), 8.25 (d, J=8.7 Hz, 2H, ArH), 7.41 (d, J=8.7 Hz, 2H, ArH), 3.93 (s, 3H, $COOCH_3$), 3.50 (s, 3H, $COOCH_3$), 2.41 (s, 3H, $ArCH_3$) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.3 (C), 167.4 (C), 160.4 (C), 147.6 (C), 143.4 (C), 139.9 (C), 133.5 (C), 131.4 (2×CH), 127.78 (C), 127.68 (C), 123.1 (2×CH), 106.9 (C), 53.3 (CH_3), 52.3 (CH_3), 13.3 (CH_3) ppm; IR (KBr): ν_{max} 3371 (br), 1739, 1679, 1521, 1374, 1229, 1035 cm^{-1}; HRMS (ESI): $[M+Na]^+$, found 402.0355. $C_{17}H_{14}NClO_7Na$ requires 402.0356.

4.2.11. Dimethyl 5-benzyl-6-chloro-4-hydroxy-3′-methylbiphenyl-2,3-dicarboxylate (**3j**)

Pale yellow solid; mp 126 °C (*n*-hexane/ether); R_f (20% EtOAc/*n*-hexane) 0.60; ^1H NMR (300 MHz, $CDCl_3$): δ 11.61 (s, D_2O-exchangeable, 1H, ArOH), 7.33–6.99 (m, 9H, ArH), 4.29 (s, 2H, $ArCH_2$), 3.89 (s, 3H, $COOCH_3$), 3.47 (s, 3H, $COOCH_3$), 2.36 (s, 3H, $ArCH_3$) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.4 (C), 167.8 (C), 159.7 (C), 141.4 (C), 138.7 (C), 137.3 (C), 136.3 (C), 134.5 (C), 130.8 (CH), 130.6 (C), 129.6 (C), 128.8 (CH), 128.6 (2×CH), 128.3 (2×CH), 127.7 (CH), 127.1 (CH), 126.2 (CH), 107.1 (C), 53.2 (CH_3), 52.0 (CH_3), 33.1 (CH_2), 21.4 (CH_3) ppm; IR (KBr): ν_{max} 3434 (br), 1745, 1671, 1439, 1346, 1232 cm^{-1}; HRMS (ESI): $[M+Na]^+$, found 447.0974. $C_{24}H_{21}ClO_5Na$ requires 447.0975.

4.2.12. Dimethyl 6-chloro-4-hydroxy-5-isopropyl-3′-methylbiphenyl-2,3-dicarboxylate (**3k**)

White solid; mp 84 °C (*n*-hexane/ether); R_f (20% EtOAc/*n*-hexane) 0.75; ^1H NMR (300 MHz, $CDCl_3$): δ 11.63 (s, D_2O-exchangeable, 1H, ArOH), 7.26 (t, J=7.5 Hz, 1H, ArH), 7.16 (d, J=7.5 Hz, 1H, ArH), 7.02 (s, 1H, ArH), 7.00 (d, J=9.6 Hz, 1H, ArH), 3.89 (s, 3H $COOCH_3$,), 3.79 (m, 1H, Me_2CH), 3.45 (s, 3H, $COOCH_3$), 2.37 (s, 3H, $ArCH_3$), 1.41 (d, J=6.9 Hz, 6H, $CHMe_2$) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.7 (C), 167.9 (C), 160.7 (C), 140.1 (C), 137.2 (C), 136.9 (C), 135.1 (C), 133.9 (C), 130.8 (CH), 130.6 (C), 128.6 (CH), 127.6 (CH), 127.2 (CH), 107.1 (C), 53.0 (CH_3), 51.9 (CH_3), 21.3 (CH_3), 19.4 (2×CH_3) ppm; IR (KBr): ν_{max} 3453 (br), 2961, 1740, 1679, 1417, 1350, 1239 cm^{-1}; HRMS (ESI): $[M+Na]^+$, found 399.0978. $C_{20}H_{21}ClO_5Na$ requires 399.0975.

4.2.13. Dimethyl 6-chloro-5-methyl-1-(pyridine-2-yl)-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**2l**)

Yellow solid; mp 112 °C (*n*-hexane/ether); R_f (20% EtOAc/*n*-hexane) 0.20; ^1H NMR (300 MHz, $CDCl_3$): δ 8.63 (m, 1H, pyridine ring H), 7.78 (dt, J=7.8, 1.8 Hz, 1H, pyridine ring H), 7.54 (td, J=7.9, 1.2 Hz, 1H, pyridine ring H), 7.32 (ddd, J=7.5, 4.8, 1.2 Hz, 1H, pyridine ring H), 5.65 (s, 1H, bridge-head H), 3.85 (s, 3H, $COOCH_3$), 3.80 (s, 3H, $COOCH_3$), 1.99 (s, 3H, $=CCH_3$) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.5 (C), 162.4 (C), 157.5 (C), 151.6 (C), 149.0 (CH), 146.9 (C), 146.6 (C), 142.5 (C), 136.8 (CH), 123.9 (CH), 122.6 (CH), 99.6 (C), 86.6 (CH), 52.46 (CH_3), 52.41 (CH_3), 12.1 (CH_3) ppm; IR (KBr): ν_{max} 1728, 1646, 1435, 1317, 1256 cm^{-1}; HRMS (ESI): $[M+Na]^+$, found 358.0458. $C_{16}H_{14}NClO_5Na$ requires 358.0458.

4.3. Opening of oxabicycloheptadiene adducts 2a and 2h

A mixture of the bicyclo adduct **2a** (0.50 g, 1.5 mmol) and $BF_3 \cdot Et_2O$ (2 mL) was heated at 60 °C for 2 h. The mixture was then cooled and treated with saturated $NaHCO_3$ solution (10 mL). It was then extracted with diethyl ether (2×10 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification by column chromatography (silica gel, *n*-hexane/EtOAc, 90:10 v/v) gave the biaryl **3a** (0.42 g, 85%). Similarly bicyclo adduct **2h** was opened in 80% yield.

Acknowledgements

We are thankful to the Council of Scientific and Industrial Research, New Delhi for a research fellowship to N.K. and a research grant.

References and notes

1. Reviews: (a) Feliu, L.; Planas, M. *Int. J. Pept. Res. Ther.* **2005**, *11*, 53–97; (b) Claeson, P.; Claeson, U. P.; Tuchinda, P.; Reutrakul, V. *Bioactive Natural Products*. Studies in Natural Products Chemistry; Elsevier Science B.V: 2002; Vol. 26, Part G, pp 881–908; (c) Bringmann, G.; Gunther, C.; Ochse, M.; Schupp, O.; Tasler, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Eds.; Springer: New York, NY, 2001; Vol. 82, pp 1–293; (d) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977–991.
2. (a) Review: Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440; (b) Baudoin, O.; Cesario, M.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **2002**, *67*, 1199–1207.
3. (a) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857–897; (b) Pu, L. *Chem. Rev.* **1998**, *98*, 2405–2494.
4. Reviews: (a) Chelma, D. S.; Zyss, J. *Nonlinear Optical Properties of Organic Molecules and Crystals*; Academic: Orlando, FL, 1987; (b) Elsenbauer, R. L.; Schacklett, L. W. In *Handbook of Conducting Polymers*; Skotheim, T. A., Ed.; Marcel Dekker: New York, NY, 1986; Vol. 1, Chapter 7.
5. *Supramolecular Chemistry*, 1st ed.; Lehn, J. M., Ed.; VCH Verlasgesellschaft: Weinheim, Germany, 1995.
6. Reviews: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047–3101; (b) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036–1045; (c) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133–173; (d) Wallace, T. W. *Org. Biomol. Chem.* **2006**, *4*, 3197–3210; (e) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211; (f) Sambasivarao Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695; (g) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.
7. (a) Wawrzyniak, P.; Heinicke, J. *Tetrahedron Lett.* **2006**, *47*, 8921–8924; (b) Freundlich, J. S.; Landis, H. E. *Tetrahedron Lett.* **2006**, *47*, 4275–4279; (c) Liu, B.; Moffett, K. K.; Joseph, R. W.; Dorsey, B. D. *Tetrahedron Lett.* **2005**, *46*, 1779–1782.
8. Reviews: (a) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384–5427; (b) Reddy, P. P.; Chu, C.-Y.; Hwang, D.-R.; Wang, S.-K.; Uang, B.-J. *Coord. Chem. Rev.* **2003**, *237*, 257–269; (c) Moreno, I.; Tellitu, I.; Herrero, M. T.; SanMartin, R.; Dominguez, E. *Curr. Org. Chem.* **2002**, *6*, 1433–1452; Some selected references: (d) Drochner, D.; Hüttel, W.; Bode, S. E.; Müller, M.; Karl, U.; Martin Nieger, M.; Steglich, W. *Eur. J. Org. Chem.* **2007**, 1749–1758; (e) Matsushita, M.; Kamata, K.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* **2005**, *127*, 6632–6640; (f) Drochner, D.; Huttel, W.; Nieger, M.; Muller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 931–933; (g) Bringmann, G.; Tasler, S. *Tetrahedron* **2001**, *57*, 331–343; (h) Sartori, G.; Maggi, R.; Bigi, F.; Grandi, M. *J. Org. Chem.* **1993**, *58*, 7271–7273.
9. (a) Bode, S. E.; Drochner, D.; Muller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5916–5920 and references cited therein; (b) Keseru, G. M.; Nogradi, M. In *Natural Products by Oxidative Phenolic Coupling: Phytochemistry, Biosynthesis and Synthesis*; Atta-ur-Rahman, Ed.; Studies in Natural Products Chemistry; Elsevier Science: New York, NY, 1998; Vol. 20, pp 263–322.
10. (a) Worm, K.; Zhou, Q. J.; Stabley, G. J.; DeHaven, R. N.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3652–3656; (b) Maegawa, T.; Kitamura, Y.; Sako, S.; Udzu, T.; Sakurai, A.; Tanaka, A.; Kobayashi, Y.; Endo, K.; Bora, U.; Kurita, T.; Kozaki, A.; Monguchi, Y.; Sajiki, H. *Chem.—Eur. J.* **2007**, *13*, 5937–5943; (c) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; OBrien, C. J.; Valente, C. *Chem.—Eur. J.* **2007**, *13*, 150–157.
11. (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238; (b) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669–8682.
12. Yamamoto, Y.; Nunokawa, K.; Ohno, M.; Eguchi, S. *Synthesis* **1996**, 949–953.
13. (a) Perkins, J. R.; Carter, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 3290–3291; (b) Ashburn, B. O.; Carter, R. G. *Org. Biomol. Chem.* **2008**, *6*, 255–257; (c) Ashburn, B. O.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2007**, *129*, 9109–9116; (d) Ashburn, B. O.; Carter, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6737–6741 and references cited therein.
14. Maggiani, A.; Tubul, A.; Brun, P. *Tetrahedron Lett.* **1998**, *39*, 4485–4488.
15. (a) Maggiani, A.; Tubul, A.; Brun, P. *Helv. Chim. Acta* **2000**, *83*, 650–657; (b) Maggiani, A.; Tubul, A.; Brun, P. *Synthesis* **1997**, 631–633; (c) Aleinik, A. F.; Adamskaya, E. V.; Novitskii, K. Y.; Soloveva, N. P.; Fadeeva, N. I.; Degtyareva, I. N.; Lapaeva, N. B.; Pershin, G. N. *Khim.-Farm. Zh.* **1980**, *14*, 49–53; *Chem. Abstr.* **1980**, *93*, 132312; (d) Ayres, D. C.; Smith, J. R. *J. Chem. Soc. C* **1968**, 2737–2740; (e) Ayres, D. C.; Smith, J. R. *Chem. Commun.* **1967**, 886–887.
16. Kappe, C. O.; Murphee, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179–14233.
17. Hayashi, Y.; Nakamura, M.; Nakao, S.; Inoue, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4079–4082 and references cited therein.
18. Dauben, W. G.; Krabbenhoft, H. O. *J. Am. Chem. Soc.* **1976**, *98*, 1992–1993.

19. Moreno, A.; Gomez, M. V.; Vazquez, E.; de la Hoz, A.; Diaz-Ortiz, A.; Prieto, P.; Mayoral, J. A.; Pires, E. *Synlett* **2004**, 1259–1263.
20. Wei, K.; Gao, H.-T.; Li, W.-D. Z. *J. Org. Chem.* **2004**, *69*, 5763–5765.
21. (a) Padwa, A.; Kenneth, R.; Crawford, K. R.; Straub, C. S.; Pieniazek, S. N.; Houk, K. N. *J. Org. Chem.* **2006**, *71*, 5432–5439; (b) Crawford, K. R.; Bur, S. K.; Straub, C. S.; Padwa, A. *Org. Lett.* **2003**, *5*, 3337–3340.
22. Pieniazek, S. N.; Houk, K. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1442–1445.
23. Ram, R. N.; Kumar, N. *Tetrahedron Lett.* **2008**, *49*, 799–802.
24. For a rare example of fully substituted *m*-chlorophenol synthesis through Alder–Rickert reaction, see: Patterson, J. W. *J. Org. Chem.* **1995**, *60*, 560–563.
25. (a) Palmer, B. D.; Thompson, A. M.; Booth, R. J.; Dobrusin, E. M.; Kraker, A. J.; Lee, H. H.; Lunney, E. A.; Mitchell, L. H.; Ortwine, D. F.; Smaill, J. B.; Swan, L. M.; Denny, W. A. *J. Med. Chem.* **2006**, *49*, 4896–4911; (b) Johnson, M. D.; Teng, M.; Zhu, J. PCT Int. Appl. 2005, CODEN: PIXXD2 WO 2005009435 A1 20050203; Application: WO 2004-IB2397 20040714. *Chem. Abstr.* **2005**, *142*, 198068; (c) Bringmann, G.; Holenz, J.; Weirich, R.; Riibenacker, M.; Funke, C.; Boyd, M. R.; Gulakowski, R. J.; Francois, G. *Tetrahedron* **1998**, *54*, 497–512; (d) Avalleri, B.; Ferrari, P.; Malabarba, A.; Magni, A.; Pallanza, R.; Gallo, G. G. *J. Antibiot.* **1987**, *40*, 49–59; (e) Jeffs, P. W.; Chan, G.; Mueller, L.; DeBrosse, C.; Webb, L.; Sitrin, R. *J. Org. Chem.* **1986**, *51*, 4272–4278.