COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Efficient synthesis of biaryl lactones by domino retro-Michael–aldol–lactonization reactions

Peter Langer,* Nehad N. R. Saleh and Ilia Freifeld
Institut für Organische Chemie der Georg-August-Universität Göttingen, Tammannstr. 2, D-37077 Göttingen, Germany. E-mail: planger@uni-goettingen.de; Fax: (+49) 551-399475

Received (in Cambridge, UK) 8th November 2001, Accepted 16th November 2001
First published as an Advance Article on the web 10th January 2002

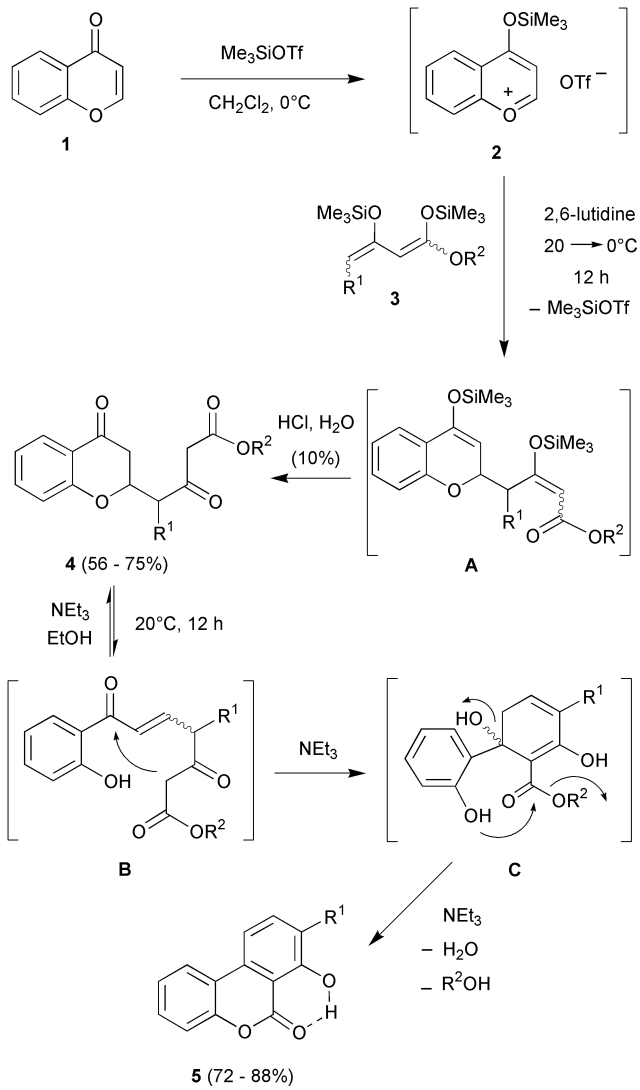
Biaryl lactones were prepared by novel domino retro-Michael–aldol–lactonization reactions of 2,3-dihydropyrans.

Functionalized biaryl lactones (dibenzo[*b*,*d*]pyran-6-ones) are present in a number of biologically relevant natural products including alternariol, autumnariol, autumnariniol and altenuisol.[1] The related benzo[*d*]naphthopyran-6-one system occurs in a variety of antibiotics and antitumor active compounds isolated from *Streptomyces*.[2] Ellagic acid and the related coruleoellagic acid represent lactonic analogues of biaryl lactones.[3] Biaryl lactones have been previously prepared by a number of methods.[4–7] Herein, we wish to report a new method for the efficient synthesis of functionalized biaryl lactones. Our approach relies on the regioselective condensation of 1,3-bis-(trimethylsilyloxy)-1,3-butadienes with benzopyrylium triflates to give functionalized 2,3-dihydrobenzopyrans, masked tetraketides, which underwent a domino retro-Michael–aldol–lactonization reaction upon treatment with base.[8]

Our initial attempts to induce a condensation of acetoacetate d[4] synthons with benzopyran **1** were unsuccessful. The reaction of **1** with the dianion of ethyl acetoacetate resulted in formation of a complex mixture. The Lewis acid (Me_3SiOTf, $TiCl_4$) mediated reaction of **1** with 1,3-bis(trimethylsilyloxy)-1,3-butadiene **3a**, an electroneutral equivalent of the dianion,[9,10] was equally disappointing. All attempts to induce a thermal Diels–Alder reaction of **1** with **3a** proved unsuccessful, presumably due to the π-donor effect of the pyran oxygen atom.[11] The problem was eventually solved by employment of the benzopyrylium triflate **2** which was generated *in situ* by treatment of **1** with Me_3SiOTf and 2,6-lutidine.[12] The reaction of **2** with diene **3a** afforded the desired 2,3-dihydrobenzopyran **4a** with very good regioselectivity (Scheme 1).† The reaction of bis-silyl enol ethers **3b–g** with benzopyrylium triflate **2** afforded the respective 2,3-dihydrobenzopyrans **4b–g** in good yields (Scheme 1, Table 1).

Our first attempts to induce a base mediated cyclization of **4a** were unsuccessful: treatment of **4a** with two equivalents of LDA or LiHMDS (−78–20 °C) afforded only complex mixtures. We have eventually found that stirring of an ethanol solution of **4a** in the presence of NEt_3 resulted in a clean transformation.† Surprisingly, the product was identified as biaryl lactone **5a**. The expected product, 1-hydroxyxanthone, was not formed. The structure of **5a** was elucidated by ^1H NMR, APT, H/H-COSY, HMBC, MS and HRMS experiments. A low field signal (^1H NMR) was diagnostic for the presence of an intramolecular hydrogen bond O–H···O.

The formation of **5a** can be explained by, what is to the best of our knowledge, the first domino retro-Michael–aldol–lactonization reaction (Scheme 1). The open-chain intermediate **B** is formed by a base induced retro-Michael reaction. The second aryl moiety is generated by an aldol reaction and subsequent elimination of water (intermediate **C**). A lactonization finally afforded the biaryl lactone **5a**. The formation of a 10-membered ring by lactonization of intermediate **B** and a subsequent transannular aldol condensation appears to be less likely (*vide infra*). Regarding the overall transformation **1** + **3a** → **5a**, three carbon atoms of the hydroxybenzene moiety of **5a**



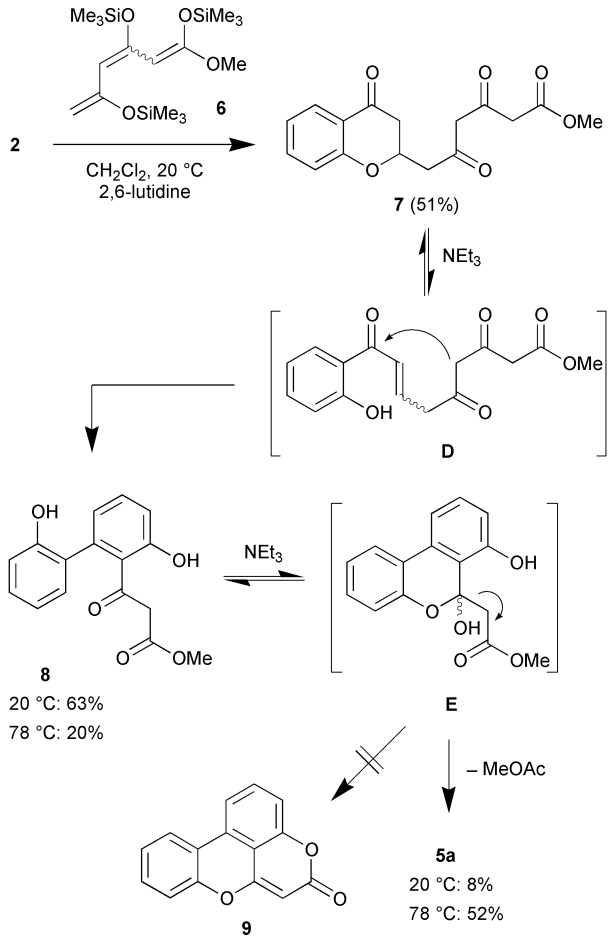
Scheme 1 Synthesis and domino retro-Michael–aldol–lactonization reactions of 2,3-dihydrobenzopyrans.

Table 1 Synthesis of 2,3-dihydropyrans **4** and biaryl lactones **5**

4/5	R^1	R^2	(**4**) [%][a]	(**5**) [%][a]
a	H	Et	75	83
b	Me	Me	66	88
c	Et	Et	64	84
d	Allyl	Et	58	72
e	Bn	Et	56	73
f	OMe	Me	70	85
g	OBn	Et	67	78

[a] Isolated yields. Products **4b–g** were obtained as mixtures of diastereomers.

DOI: 10.1039/b110236m



Scheme 2 Reaction of tris-silyl enol ether **6** with **2**.

are derived from carbons C-2, C-3 and C-4 of bis-silyl enol ether **3a** and from the three non-benzene carbons of **1**. The lactone carbon of **5a** stems from carbon C-1 of **3a**.

First results related to the preparative scope of the new domino reaction are described next. Treatment of pyrans **4b**, **4c**, **4d** and **4e** with NEt_3 afforded the methyl, ethyl, allyl and benzyl substituted biaryl lactones **5b**, **5c**, **5d** and **5e**, respectively (Table 1). The reaction of **4f** and **4g** with NEt_3 gave the methoxy and benzyloxy substituted biaryl lactones **5f** and **5g**, respectively. All products were obtained in very good yields (72–88%).

The reaction of **2** with tris-silyl enol ether **6** afforded the masked pentaketide **7** in 51% yield (Scheme 2). Treatment of **7** with NEt_3 at 20 °C afforded the functionalized biaryl **8** in 63% yield *via* the open-chain intermediate **D**. This result supported our initial assumption that the formation of biaryl lactones **5** indeed proceeded by the mechanism as depicted in Scheme 1 rather than by initial lactonization. Biaryl **8** was isolated only as a side-product in 20% yield when the reaction of **7** with NEt_3 was carried out under reflux. Unexpectedly, the major product was biaryl lactone **5a** which was formed in 52% yield by formation of a hemiketal (intermediate **E**) and subsequent retro-aldol reaction (extrusion of methyl acetate).

P. L. thanks Professor A. de Meijere for his support. Financial support by the Fonds der Chemischen Industrie e. V. (Liebig scholarship and funds for P. L.) and by the Deutsche Forschungsgemeinschaft (Heisenberg scholarship for P. L.) is gratefully acknowledged.

Notes and references

† *Synthesis* of **4a**: To chromone **1** (500 mg, 3.42 mmol) was added Me_3SiOTf (0.80 ml, 4.4 mmol) at 20 °C. After stirring for 1 h, CH_2Cl_2 (7 ml), 2,6-lutidine (0.52 ml, 4.4 mmol) and **3a** (1.22 g, 4.4 mmol) were added at 0 °C. The mixture was stirred for 12 h at 20 °C and subsequently poured into an aqueous solution of hydrochloric acid (10%). The organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic layers were washed with water, dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ether–petroleum ether = 1:10 → 1:1) to give **4a** as a colourless solid (708 mg, 75%). ^{1}H NMR (keto–enol = 9:1, $CDCl_3$, 250 MHz): δ = 1.07 (t, J = 6.5 Hz, 3 H, CH_3), 2.59 (m, 2 H, chain CH-CH_2), 2.78 (dd, ^2J = 17.2, ^3J = 5.3, 1 H, ring CH_2), 3.02 (dd, ^2J = 17.2, ^3J = 7.1, 1 H, ring CH_2), 3.38 (s, 2 H, chain CH_2), 4.00 (q, J = 6.5 Hz, 2 H, OCH_2), 4.74 (m, 1 H, C*H*-CH_2, keto tautomer), 4.65 (m, C*H*-CH_2, enol tautomer), 4.95 (s, =C*H*-, enol tautomer), 6.70-6.85 (m, 2 H, Ar), 7.25 (t, J = 7.8 Hz, 1 H, Ar), 7.62 (dd, ^3J = 7.8 Hz, ^4J = 1.5, 1 H, Ar). ^{13}C NMR ($CDCl_3$, 62.5 MHz, only keto tautomer listed): δ = 13.53 (CH_3), 41.70, 46.77, 49.13 (CH_2), 60.86 (OCH_2), 72.92 (CH), 117.34 (CH), 120.29 (C), 121.02, 126.29, 135.50 (CH), 160.46, 166.30, 190.76, 198.97 (C). IR (KBr): $\tilde{\nu}$ = 3427 (w), 3005 (m), 2991 (m), 2965 (m), 2948 (m), 2920 (m), 2906 (m), 1737 (s), 1707 (s), 1607 (s), 1578 (m), 1474 (s), 1459 (s), 1403 (s), 1316 (s), 1302 (s), 1278 (s), 1153 (s) cm^{-1}. MS (70 eV, *m/z*): 276 (M^+, 20), 231 (3), 203 (7), 147 (100); the exact molecular mass for $C_{15}H_{16}O_5$ *m/z* = 276.0997 ± 2 mD (M^+) was confirmed by HRMS (EI, 70 eV).

Synthesis of **5a**: An ethanol solution (6 ml) of **4a** (150 mg, 0.54 mmol) and NEt_3 (60 mg, 0.59 mmol) was stirred for 12 h at 20 °C. To the solution was added an aqueous solution of hydrochloric acid (1 M) and ether (50 ml). The organic and the aqueous layer were separated and the latter was extracted with ether (3 × 100 ml). The combined organic layers were washed with water, dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, ether–petroleum ether = 1:5) to give **5a** as a colourless solid (95 mg, 83%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.06 (d, J = 8.2 Hz, 1 H, Ar), 7.30-7.40 (m, 2 H, Ar), 7.47 (dt, J = 5.5, J = 1.5 Hz, 1 H, Ar), 7.56 (d, J = 8.0 Hz, 1 H, Ar), 7.70 (t, J = 8.0 Hz, 1 H, Ar), 8.03 (dd, J = 5.5, J = 1.5 Hz, 1 H, Ar), 11.36 (s, 1 H, OH). ^{13}C NMR (APT, $CDCl_3$, 50.3 MHz): δ = 106.10 (C), 112.14, 116.46, 117.68 (CH), 118.25 (C), 123.32, 125.15, 130.59 (CH), 135.19 (C), 137.26 (CH), 150.50, 162.43, 165.39 (C). MS (EI, 70 eV): *m/z* = 212 (M^+, 100), 184 (10); the exact molecular mass for $C_{13}H_8O_3$ *m/z* = 212.0473 ± 2 mD (M^+) was confirmed by HRMS (EI, 70 eV). Anal.: Calcd. for $C_{13}H_8O_3$: C 73.58, H 3.80. Found: C 73.34, H 3.98%. All new compounds gave satisfactory spectroscopic and analytical and/or high resolution mass data.

1 Alternariol: H. Raistrick, C. E. Stilkings and R. Thomas, *Biochemistry*, 1953, **55**, 421; autumnariol and autumnariniol: C. Tamm, *Arzneim.-Forsch.*, 1972, **22**, 1776; altenuisol: R. W. Pero, D. Harvan and M. C. Blois, *Tetrahedron Lett.*, 1973, 945.
2 For references related to defucogilvocarcin V, gilvocarcins, chrysomycins and ravidomycins, see: B. I. Alo, A. Kandil, P. A. Patil, M. J. Sharp, M. A. Siddiqui and V. Snieckus, *J. Org. Chem.*, 1991, **56**, 3763, references 6–10.
3 J. M. Sayer, Y. Haruhiko, A. W. Wood, A. H. Conney and D. M. Jerina, *J. Am. Chem. Soc.*, 1982, **104**, 5562; Y. A. G. P. Gunawardana, N. S. Kumar and M. U. S. Sultanbawa, *Phytochemistry*, 1979, **18**, 1017.
4 W. R. H. Hurtley, *J. Chem. Soc.*, 1929, 1870. For other approaches, see reference 2.
5 T. M. Harris and J. V. Hay, *J. Am. Chem. Soc.*, 1977, **99**, 1631.
6 G. Bringmann and H. Reuscher, *Tetrahedron Lett.*, 1989, 5249.
7 G. Bringmann, J. Hinrichs, T. Pabst, P. Henschel, K. Peters and E.-M. Peters, *Synthesis*, 2001, 155 and references cited therein.
8 For a review of sequential reactions, see: L. F. Tietze and U. Beifuss, *Angew. Chem.*, 1993, **105**, 137; L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131; for domino reactions, see: L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115.
9 T.-H. Chan and P. Brownbridge, *J. Chem. Soc., Chem. Commun.*, 1979, 578; T.-H. Chan and P. Brownbridge, *J. Am. Chem. Soc.*, 1980, **102**, 3534; G. A. Molander and K. O. Cameron, *J. Am. Chem. Soc.*, 1993, **115**, 830.
10 P. Langer, T. Schneider and M. Stoll, *Chem. Eur. J.*, 2000, **6**, 3204.
11 For [4 + 2] cycloadditions of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with chloro-benzoquinones, see for example: G. Roberge and P. Brassard, *Synthesis*, 1981, 381.
12 For the generation of silyloxy-1-benzopyrylium triflates and their reaction with silyl enol ethers, see: H. Iwasaki, T. Kume, Y. Yamamoto and K.-Y. Akiba, *Tetrahedron Lett.*, 1987, 6355; Y.-G. Lee, K. Ishimaru, H. Iwasaki, K. Ohkata and K. Akiba, *J. Org. Chem.*, 1991, **56**, 2058; for the generation of thiobenzopyrylium salts, see: U. Beifuss, M. Tietze and H. Gehm, *Synlett*, 1996, 182.