Pergamon

Tetrahedron Letters 39 (1998) 1545–1548

TETRAHEDRON
LETTERS

Synthesis and Structure of a Novel Twofold Lactone-Bridged Ternaphthyl[1]

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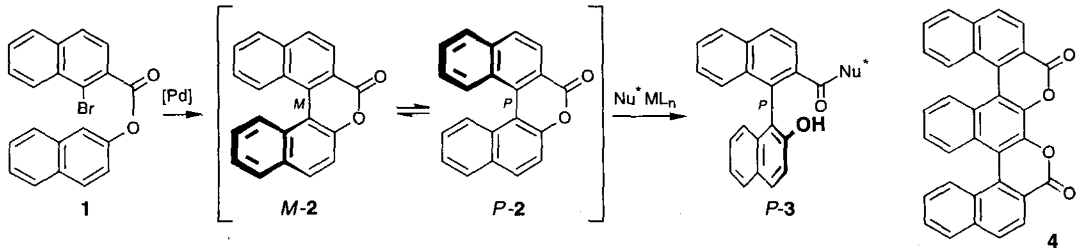
Received 4 December 1997; accepted 23 December 1997

Abstract: The synthesis of the sterically distorted ternaphthyl-bislactone **4**, by consecutive palladium-catalyzed coupling reactions of ester-type pre-fixed aryl segments, is described. The *meso*-form of this novel teraryl was found to be energetically favored as demonstrated by semiempirical and *ab initio* calculations. It is also found in the crystal, as shown by X-ray investigations.

Ter- and polyaryl materials have been the focus of recent attention owing to their utility in the preparation of liquid crystals,[2] polymers,[3] and molecular recognition hosts.[4,5] Moreover, ter- and quateraryl systems occur in nature, like the butlerins from the lichen *Relicina connivens*[6] and the anti-HIV michellamines from the tropical liana *Ancistrocladus korupensis*.[7] For directed, *i.e.* atropisomer-selective biaryl synthesis, lactone-bridged biaryls like **2**,[8] as easily built up by intramolecular coupling of ester-type pre-fixed aromatic moieties as in **1**, have proved to be most useful intermediates (see Scheme 1). They are configuratively unstable, giving rise to interconverting atropo-enantiomers (here *M*-**2** ⇌ *P*-**2**), but can be ring opened atropodiastereo- or enantioselectively by chiral (metallated) nucleophiles[9-11] to yield the axially stable target biaryl *P*-**3** (or, optionally, the *M*-enantiomer). This preparatively useful and stereochemically interesting concept has been applied to the synthesis of a broad series of natural and unnatural biaryl products, among them promising antimalarial naphthylisoquinoline alkaloids[12,13] and nerve-growth stimulating mastigophorene analogs.[14] In this paper, we report on the first synthesis of an extended biaryl lactone system, the twofold lactone-bridged ternaphthyl **4**, and on the experimental and quantumchemical investigation of its structure.



Scheme 1. Stereoselective biaryl synthesis using the 'lactone concept', and the target teraryl **4**.

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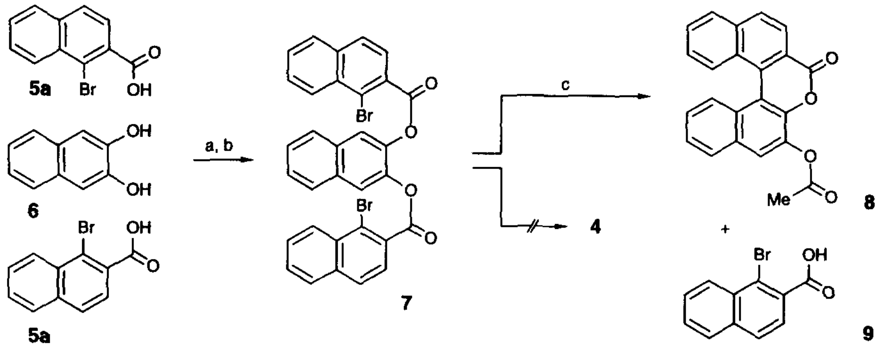
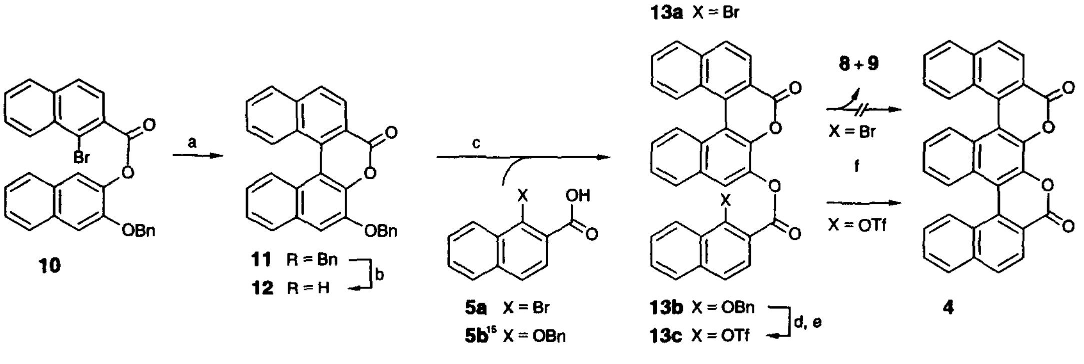
PII: S0040-4039(98)00022-7

In analogy to the synthesis of **2**, the easiest-possible strategy to build up **4** should be a *twofold* intramolecular biaryl coupling of **7** (Scheme 2). This dibromo diester[15] was prepared from 2,3-dihydroxynaphthalene (**6**) and 1-bromo-2-naphthoic acid (**5a**).[16] Under various conditions, only the mono-coupled product **8**,[15] with but one axis successfully constructed and the other ester linkage cleaved to the bromoacid **9**, was obtained. Similar cleavage reactions had been observed previously in other cases.[17,18]



Scheme 2. Attempted rational approach to the synthesis of **4**. Reaction conditions: a) $SOCl_2$; b) NaH, CH_2Cl_2, 0°C, 87% from **5a**; c) $Pd(OAc)_2$, PPh_3, NaOAc, dimethylacetamide (DMA), 130°C, 20%.

The biaryl axes were therefore planned to be built up *consecutively*. For this, as an alternative to the (wasteful) synthesis of **8**, its *O*-benzyl analog **11**[15] was prepared by intramolecular coupling of monoester **10**[15] as obtained from **5a** and the known[19] monobenzyl ether of **6** (Scheme 3). After removal of the benzyl protective group, renewed esterification with **5a** yielded **13a**,[15] the assumed intermediate in the unsuccessful double biaryl coupling of **7** (see above). Regrettably, even this defined monoester failed to undergo a second biaryl formation, but again gave the same cleavage products **8** and **9** as previously obtained from the diester **7**. Because of the excellent quality of the triflate rather than the bromide leaving group in such coupling reactions,[20] we analogously prepared the related ester **13c**[15] *via* **13b**.[15] This compound indeed underwent the second biaryl coupling step to give the desired teraryl **4**,[15] which displays a brilliant blue-green fluorescence.



Scheme 3. Construction of **4** by consecutive coupling steps of **10** and **13c**. Reaction conditions: a) $Pd(OAc)_2$, PPh_3, NaOAc, DMA, 100°C, 76%; b) BCl_3, CH_2Cl_2, 0°C, 92%; c) $(COCl)_2$, NEt_3, THF, 0°C, 91%; d) BCl_3, CH_2Cl_2, 0°C; e) Tf_2O, DMAP, py, CH_2Cl_2, 0°C, 67% from **13b**; f) $Pd(OAc)_2$, PPh_3, NaOAc, DMA, 130°C, 37% for **13c** → **4**.

Of particular interest was the 3D structure of **4**. For this unprecedented teraryl-bislactone with its two stereogenic axes, three possible stereoisomers are imaginable: the two enantiomeric C_2-symmetric *P,P*- and *M,M*-forms, *i.e.* with the two axes homochiral (see Fig. 1), and *M,P*-**4**, the achiral *meso*-form, with the two axes differently configurated. In NMR, the compound presents itself as a single species, which, given the relatively slow interconversion for **2**,[8] may mean that **4** occurs either as an enantiomeric mixture of the two C_2-symmetric forms, *P,P*- and *M,M*-**4**, or as the *meso*-form *M,P*-**4**. Semiempirical[21] (AM 1 and PM 3) and *ab initio*[22] calculations (Hartree Fock) predict the *meso*-form *M,P*-**4** to be energetically favored by 15.4-19.3 kJ/mol over the C_2-symmetric helically distorted enantiomers *P,P*-**4** und *M,M*-**4** in the gas phase (Table 1). This would correspond to a 99.6:0.4 to 99.9:0.1 predominance of the *meso*-form, the C_2-symmetric forms apparently therefore not being visible in NMR.

Table 1. Calculated semiempirical energies ΔH_f [kJ/mol] and *ab initio* energies *E* [Hartrees], and relative heats of formation $\Delta\Delta H_f$ [kJ/mol] of *M,P*-**4** and *P,P*-**4**.

Method		*M,P*-**4**	*P,P*-**4**	$\Delta\Delta H_f$
AM1	ΔH_f	-963.35	-948.00	-15.35
PM3	ΔH_f	-1029.23	-1011.65	-17.58
B3LYP/6-31G*//RHF/6-31G*	*E*	-1529.55938360	-1529.55205667	-19.25

The semiempirical ΔH_f values and the *ab initio* energies *E* are ZPVE corrected (1 Hartree = 2627.26 kJ/mol)

Crystals suited for an X-ray diffraction analysis[23] were grown from dichloromethane, with the solvent being a stoichiometric constituent of the crystal (see Fig. 1). The crystal structure analysis clearly confirms the anticipated constitution and reveals **4** to crystallize out in a remarkably distorted *meso*-form.

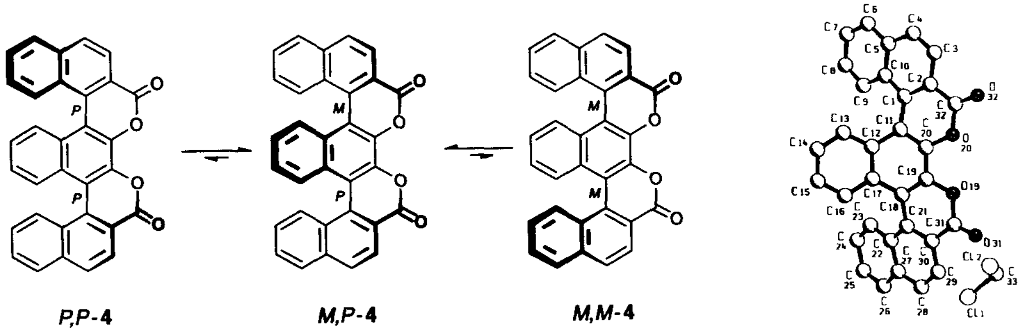


Fig. 1. Presumable interconversion of the three possible atropisomeric forms of **4** and structure of *M,P*-**4**·CH_2Cl_2 in the crystal.

The atroposelective ring cleavage of **4**, as well as the preparation of even higher lactone-bridged oligo- and polyaryls, is under investigation.

ACKNOWLEDGEMENTS

This work was supported by the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 347 "Selektive Reaktionen Metall-aktivierter Moleküle"). We are indebted to Dr. B. Schöner and Dr. S. Harmsen for orienting work in this field and Mrs. P. Henschel for valuable technical assistance.

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21. Performed on SGI IRIS INDIGO R4000/R440 workstations with the program package VAMP 6.2.
22. Performed on a Fujitsu VPP 700 computer using the Gaussian 94 program.
23. Cell data for **4**: $C_{32}H_{16}O_4 \cdot CH_2Cl_2$, monoclinic, space group $P2_1/n$, a = 1073.0(1) pm, b =1326.0(1) pm, c = 1745.7(2) pm, β = 101.809(7)°. Additional data for this structure have been submitted to the Cambridge Crystallographic Data Centre.