



Synthesis, separation, and structural analysis of planar chiral carboxy-substituted [2.2]metacyclophanes



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ARTICLE INFO

Article history:

Received 11 January 2013
Received in revised form 28 February 2013
Accepted 18 March 2013
Available online 22 March 2013

Keywords:

[2.2]Metacyclophane
Planar chirality
LiNK metalation
Structural analysis

ABSTRACT

A two-step synthesis of carboxy-functionalized planar chiral [2.2]metacyclophanes from *m*-xylenes is described. Both transformative steps utilize LiNK metalation conditions (BuLi, KO*t*-Bu, TMP(H)) for *m*-xylene benzylic deprotonation with subsequent in situ oxidative C–C coupling. Inclusion of the carboxy substituents at either C4, or C4 and C14, renders the [2.2]metacyclophanes planar chiral and the structural analysis of both substitution patterns has been achieved with X-ray crystallography and NMR spectroscopy. The C4 mono- and C4/14 di-substituted carboxylic acid methyl ester racemates were readily separated by analytical and preparative chiral HPLC and their inversion barriers measured in heptanes at 373 K at 125.3 kJ/mol and 130.9 kJ/mol, respectively. The facile synthesis, separation, and high inversion barriers of planar chiral [2.2]metacyclophanes present an opportunity for their investigation as chiral catalysts and ligands, which to date has yet to be explored.

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1. Introduction

The unique and intriguing properties of constrained [2.2]cyclophanes has led to a continued interest in them since the first report by Brown and Farthing in 1949.¹ 'Phane' molecules template interactions between layered π -systems within constrained three-dimensional architectures, and this unique feature has been extensively investigated and exploited.² In this context, the [2.2]paracyclophanes have seen a recent resurgence of interest, notably as planar chiral scaffolds for asymmetric catalysis.³ Among the other potential chiral cyclophane structures, the planar chirality of [2.2]metacyclophanes has received scant attention, with the synthesis of only a few chiral derivatives described.⁴ Thermodynamic and kinetic studies have shown that for the [*n.n*]metacyclophanes, only the most constrained [2.2]metacyclophanes have an inversion barrier high enough to permit resolution of conformationally stable enantiomers.⁵ However, few examples of optical resolution^{4a,6} and crystal structure determination⁷ of planar chiral [2.2]metacyclophanes have been reported to date.

We recently reported that challenging benzylic metalations can be achieved with excellent regioselectivity by means of a mixed Li/K metal TMP amide (LiNK metalation conditions) generated in situ by the reagent triad BuLi/KO*t*-Bu/TMP(H).⁸ In the course of our studies, aimed to exploit further synthetic applications of LiNK metalation conditions, we described a two-step general approach

to planar chiral [2.2]metacyclophanes, starting from inexpensive commercially available substituted *m*-xylenes.⁹ Our strategy employs a selective LiNK benzylic metalation with an in situ oxidative coupling reaction¹⁰ for both synthetic operations. In order to render the [2.2]metacyclophane scaffold planar chiral, the symmetry plane bisecting the cyclophane ring must be differentiated by substitution in either positions C4, or C4 and C14 (Fig. 1), which renders the original C₂ symmetry lost and planar chirality created.⁴ In this report, the synthesis, structural characterization, enantiomer separation, and configurational stability of potentially useful optically active mono- and di-carboxy[2.2]metacyclophanes are described.

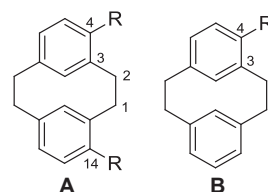


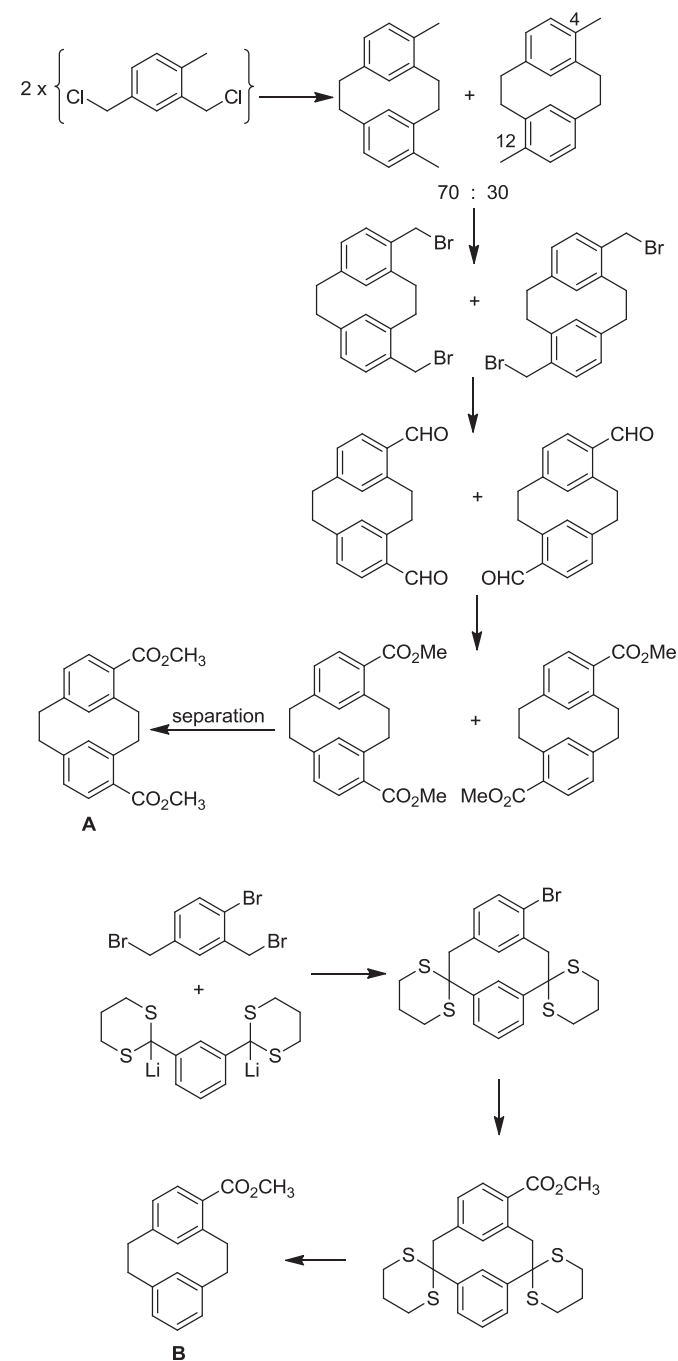
Fig. 1. Planar chiral [2.2]metacyclophanes.

2. Results and discussion

The preparation of planar chiral carboxy[2.2]metacyclophane derivatives has been previously described in the literature via lengthy multi-step approaches. For example, the synthesis of [2.2]metacyclophane-4,14-dicarboxylic acid methyl ester (Fig. 1A, R/R=CO₂CH₃, Scheme 1 top) has been accomplished by conversion

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of the corresponding 4,14-dimethyl cyclophane, obtained as a mixture with the 4,12-isomer after chloromethylation of toluene followed by Wurtz coupling.^{4c,11} Bromomethylation and subsequent Sommelet reaction led to the corresponding dialdehyde derivatives, which were further transformed into a mixture of diesters. Chromatography separation of the unwanted achiral 4,14-isomer provided the target metacyclophane type A.^{4c,11} Mono-substituted 4-carboxylic acid ester (Fig. 1B, R=CO₂CH₃, Scheme 1 bottom) has been prepared by a six-step synthesis.^{4a} In this case, the metacyclophane skeleton was constructed by di-alkylation of di-lithiated isophthalaldehyde bis-dithiane with 1-bromo-2,4-bis(bromomethyl)benzene. Lithium–bromine exchange (of aryl-bromide) followed by CO₂ quench and esterification with diazomethane introduced an aryl ester group. Subsequent reductive



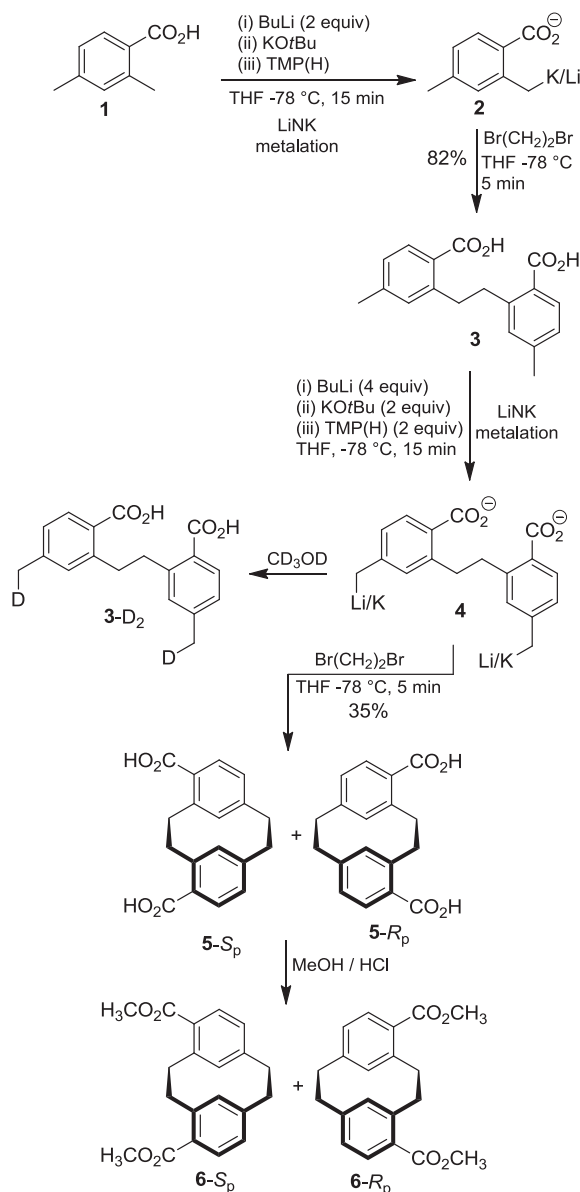
Scheme 1. Existing routes to substituent pattern types A and B for [2.2]metacyclophanes.

cleavage of dithianes with Raney Ni catalyst led to the targeted cyclophane type B. Following saponification, both mono- and bis-carboxy racemic mixtures could be resolved via their diastereomeric salts with (+)-1-phenylethylamine.^{4a,12}

LiNK metalation conditions with in situ oxidative coupling offers a facile general approach to the [2.2]metacyclophanes.⁹ To access carboxy-substituted planar chiral derivatives, two inexpensive starting materials *m*-xylene and 2,4-dimethylbenzoic acid are required. From these two reagents, the C4 carboxy and C4/14 dicarboxy derivatives were selected for synthesis as benchmark examples of this class of planar chiral scaffold.

2-Methyl metalation of 2,4-dimethylbenzoic acid **1** under LiNK conditions⁹ for 15 min (additional equivalent of BuLi included for deprotonation of the carboxylic acid) led to the dianion **2**, which underwent oxidative homocoupling after addition of 1,2-dibromoethane, leading to the corresponding 2,2'-(ethane-1,2-diyl)bis(4-methylbenzoic acid) **3** in 82% yield (Scheme 2).

Compound **3** represents a challenging substrate to selectively achieve a di-benzylic metalation to generate the required tetra-



Scheme 2. Iterative LiNK/oxidative coupling synthesis of [2.2]metacyclophane-4,14-dicarboxylic acid **5** and corresponding dimethyl ester **6**.

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