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Asymmetric synthesis of novel spirocycles via a chiral phosphoric acid catalyzed desymmetrization

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ABSTRACT

A straightforward method for the asymmetric preparation of novel lactone and lactam spirocycles is described. An initial desymmetrization via a chiral Brønsted acid yields enantioenriched lactones which readily undergo a second cyclization to give the desired spirocycle.

1. Introduction

Spirocycles are important natural products,[1] chiral ligands,[2] drug scaffolds,[3] and optoelectronics.[4] Spirolactones are an important class of spiro compounds (Figure 1). Drospirenone (**1**), is a synthetic spirolactone analog of progesterone and is used as an oral contraceptive (marketed as Yasmin in the US).[5] Drospirenone contains a tertiary carbon spiro center which is prevalent in many other biologically interesting or naturally occurring spirolactones.[6] All carbon spiro centers as seen in spirosesquiterpenes **2** and **3** are much less common.[7-8] We predict that a straightforward enantioselective synthesis of these types of scaffolds would lead to their increased use and study as a new core structure for development.[9]

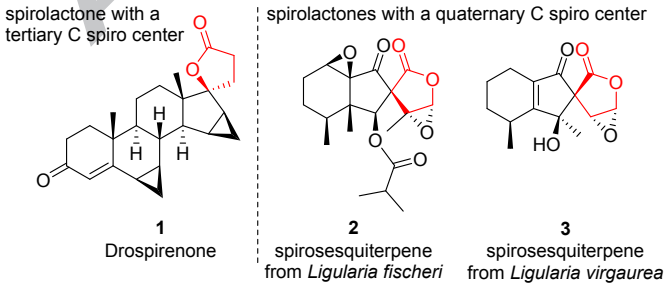
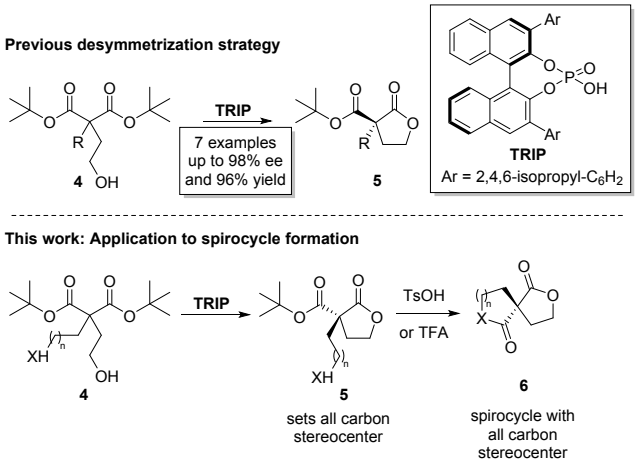


Figure 1. Spirocyclic lactones.

We have recently developed a novel asymmetric cyclization strategy for the formation of chiral lactones with all carbon quaternary stereocenters in up to 98% ee and 96% yield (Scheme 1).[10-11] This desymmetrization method utilized a chiral phosphoric acid catalyzed intramolecular lactonization. DFT calculations of the analogous kinetic resolution indicate that the reaction proceeds via a step-wise mechanism promoted by dual activation of both the carbonyl via the Brønsted acidic proton and the hydroxyl group via the Lewis acidic oxygen of the chiral phosphoric acid.[12]

Herein we disclose the synthesis of novel spirocyclic scaffolds via an analogous protocol. We envisioned that the desymmetrization of diesters such as **4** with two alkyl chains that contain nucleophiles would proceed to yield an enantioenriched lactone that could undergo a second cyclization with a general acid (Scheme 1). Formation of the γ-lactone during the initial enantioselective cyclization is proposed due to previous indications of higher enantioselectivities and shorter reaction times for the cyclization of 5-membered ring lactones.[11]

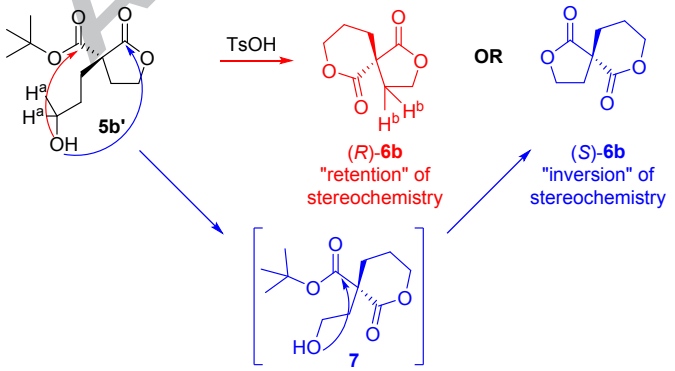


Scheme 1. All carbon spirocycle strategy.

2. Results

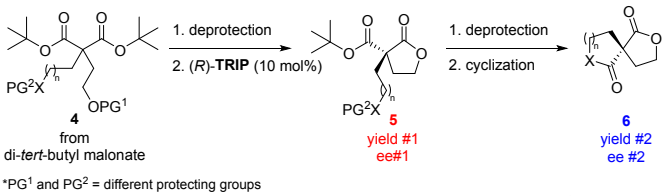
A series of basic spirocyclic scaffolds were prepared using the general strategy outlined above (Table 1). Remarkably, other than compound **6a**,[13] the prepared spirocycles are novel even in their racemic form. Initially, diesters **4** were prepared via two alkylations from di-*tert*-butyl malonate. Deprotection of protecting group #1 (PG^1) yielded the free alcohol which, when cyclized with **TRIP** gave the enantioenriched γ-lactones **5** in modest to good yields and enantiopurities. Deprotection of protecting group #2 (PG^2) followed by cyclization with either trifluoroacetic acid or *para*-toluene sulfonic acid yielded the desired spirocycles **6**.[14] In general, a moderate drop in ee was seen during this second cyclization, likely due to some scrambling of the stereocenter in the second cyclization (see further discussion below). Spirocycle **6a** was obtained in racemic form, even after a nearly enantiopure first cyclization. This likely is due to the fast cyclization of **5a** under deprotection conditions. Spirocycle **6d** was prepared via cyclization of precursor **5d** with trifluoroacetic acid (*para*-toluene sulfonic acid is not effective at inducing cyclization). Careful monitoring of the reaction indicates that this cyclization goes through a carboxylic acid intermediate. Recrystallization of spirocycles leads to an increase in optical purity as seen in spirocycle **6d** which goes from 60→85% ee in one recrystallization. Lactone/lactam spirocycle **6e** was formed via a CDI (1,1′-Carbonyldiimidazole) coupling reaction of the carboxylic acid formed upon saponification of **5e**. The more substituted spirocycle **6f**, containing a dihydro benzopyrone ring was prepared in good enantiomeric purity (72% ee). The absolute stereochemistry of spirocycle **6e** was determined by x-ray crystallography[15] and all others were assigned based on analogy.

There are two potential pathways for the second cyclization and formation of the spirocycle. The first, is that the second cyclization takes place with "retention" of stereochemistry via the second nucleophile reacting with the remaining *tert*-butyl ester (see red arrows, **5b'**→(*R*)-**6b** in Scheme 2). Another possible pathway is that the second nucleophile initially attacks the lactone ester to form intermediate **7**, which is followed by cyclization to yield the "inverted" spirocyclic product (see blue arrows, **5b'**→**7**→(*S*)-**6b** in Scheme 2). To probe these potential pathways we monitored the cyclization of **5b'** via ^{1}H NMR.[16] Figure 2 shows a snapshot of this experiment. The signal at 3.6 ppm represents protons *a* (H^a) in **5b'** and the signal at 2.9 ppm represents protons *b* (H^b) in **6b**. This time-dependent NMR suggests direct conversion of **5b'** to **6b**. We postulate that the decrease in ee seen in the second cyclization is due to trace and undetectable by ^{1}H NMR, formation of **7** under the longer reaction times required for optimized spirocycle formation yields.

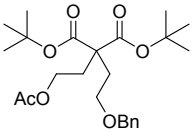
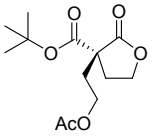
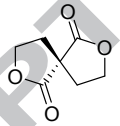
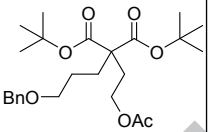
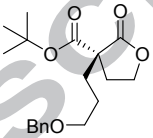
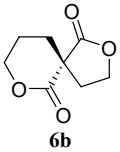
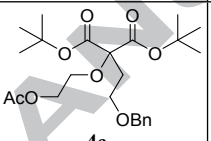
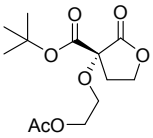
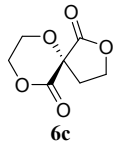
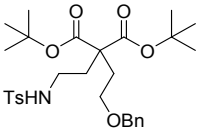
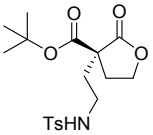
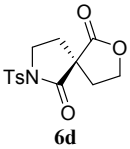
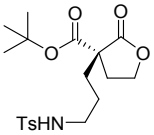
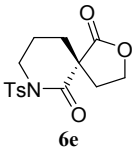
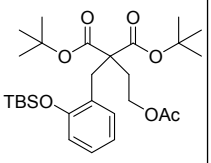
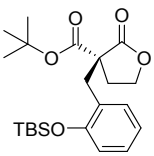
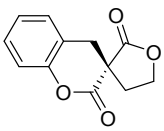


Scheme 2. Mechanistic pathway considerations.

Table 1. Results



*PG^1 and PG^2 = different protecting groups

 **4a**	 **5a** 39% yield (from **4a**) 99% ee	 **6a** 92% yield (from **5a**) 0% ee
 **4b**	 **5b** 49% yield (from **4b**) 81% ee	 **6b** 78% yield (from **5b**) 63% ee
 **4c**	 **5c**[a] 79% yield (from **4c**) 41% ee	 **6c** 60% yield (from **5c**) 24% ee
 **4d**	 **5d**[a] 88% yield (from **4d**) 84% ee	 **6d** 85% yield (from **5d**) 60% then 85% ee after recrystallization
	 **5e** 56% yield (from **5b'**) 81% ee	 **6e** 41% yield (from **5e**) 70% ee
 **4f**	 **5f** 54% yield (from **4f**) 76% ee	 **6f** 34% yield (from **5f**) 72% ee

[a](*S*)-TRIP was used in cyclization.

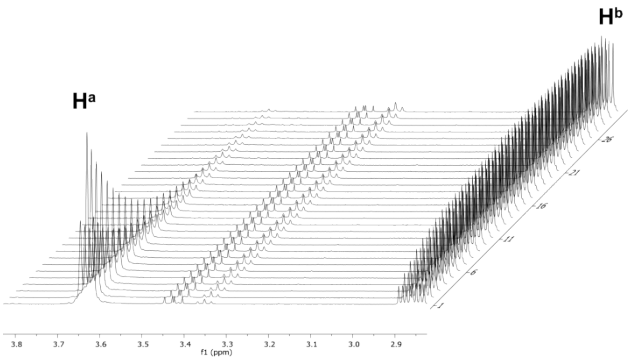


Figure 2. ^{1}H NMR experiment.

3. Conclusion

In conclusion, we describe a straightforward method for the synthesis of novel enantioenriched all-carbon spirocycles. Formation of the first lactone ring via an asymmetric Brønsted acid catalyzed desymmetrization of dialkylated diesters is followed by a second cyclization utilizing a general acid. This method offers access to new scaffolds that are likely find use in future applications.

Acknowledgments

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Supplementary Material

Supplementary data for this work can be found online at https://xxxx. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1884802. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).

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14. A one pot cyclization of the corresponding diol of **4b** was attempted with 10 mol% **TRIP**, however only recovered starting material was obtained.

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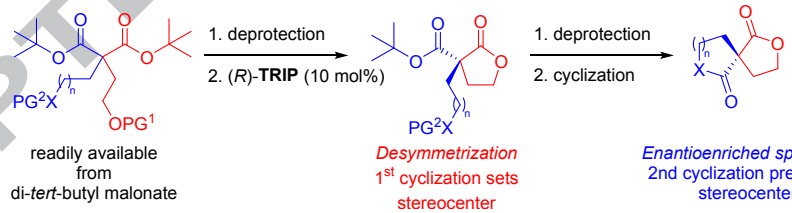

15. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1884802. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).
16. Compound **5b** (21 mg, 0.085 mmol) and TsOH (49 mg, 0.25 mmol) in 5.9 mL of a 0.1 M stock solution of 1,2,4,5-tetrachloro-3-nitrobenzene. See SI for more details.

Graphical Abstract

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- Formation of novel enantioenriched spirolactones

- Chiral Brønsted acid catalyzed desymmetrization
- New all-carbon scaffolds