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Kinetic Resolution in a Bridgehead Lithiation Mediated by a Chiral Bis-lithium Amide: Assignment of the Absolute Configuration of Clusianone

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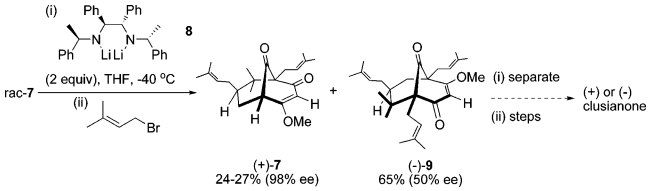

A chiral base kinetic resolution of an advanced bicyclic intermediate enabled access to the polyprenylated phloroglucinol natural product (+)-clusianone in enantiomerically pure form. X-ray structure determination of another product obtained by the same method then allowed the absolute stereochemistry of (+)-clusianone to be assigned.

Plants and trees of the family Clusiaceae (Guttiferae) are a rich source of polyprenylated acylphloroglucinols (PPAPs), characterized by a bicyclo[3.3.1]nonanetrione core structure bearing additional acyl and prenyl substituents, e.g., hyperforin (**1**), clusianone (**2**), and nemorosone (**3**) Figure 1.[1]

This family of compounds has attracted substantial synthetic interest, partly due to the challenge associated with the assembly of such highly substituted and oxygenated bridged structures and partly due to the diverse medicinal potential exhibited by many members, including anti-HIV, anti-cancer, and antidepressant activities.[2]

The idea of constructing either naturally occurring PPAPs or unnatural derivatives by appending substituents to a common [3.3.1] trione core system is an attractive one in terms of accessing diverse structures for probing the SAR in these systems. In principle, regioisomeric structures such as **2** and **3** could be accessed very effectively this way. In this context, we recently reported the first synthesis of racemic clusianone, which involved annulation of an enol ether **4**/**5** with malonyl dichloride (Effenburger reaction) to give a core structure **6**.[3,4] This

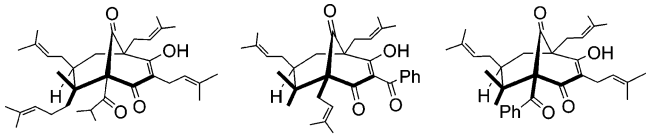

FIGURE 1. Representative PPAPs.

compound, in the form of a derived enol ether **7**, was transformed into clusianone by means of regioselective lithiation, first at C-5 and then at C-3, Scheme 1.

During this study, we noted that the absolute stereochemistry of clusianone had not been assigned.[5] According to the excellent review of this area by Ciochina and Grossman,[1] the absolute configurations of only three members of the PPAP family have been determined experimentally; most notably, hyperforin has the structure shown above, as established by X-ray crystallography of a derived enol ester.[6] In our previous paper, we arbitrarily represented clusianone in the same enantiomeric series as hyperforin, as shown above. The situation is further complicated by the fact that a number of PPAPs have been isolated in either enantiomeric form, depending upon the source species.

Since for exploration of biological activity profiles a knowledge of the absolute stereochemistry of chiral materials is of great importance, we decided to investigate this issue with respect to clusianone. Our idea was to carry out kinetic resolution of racemic **7** using a chiral base and then use X-ray structure determination to assign intermediates that would then be correlated with the natural material by comparison of specific rotation data. Herein we describe our preliminary results, which enable unambiguous assignment of the absolute stereochemistry of (+)-clusianone *as the enantiomer of the structure shown in Figure 1.*

We initially established that kinetic resolution of **7** was possible by metalation with the bis-lithium amide **8**, Scheme 2.[7,8]

The use of 2 equiv of base **8** appears necessary to achieve levels of conversion of about 60−70%. Under these conditions the prenylated product (−)-**9** was isolated in 65% yield and with an ee of about 50%, whereas the recovered starting material, (+)-**7**, isolated in 24−27% yield was essentially enantiomeri-

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(1) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963−3986.
(2) Verotta, L. *Phytochem. Rev.* **2002**, *1*, 389−407.
(3) Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. *Org. Lett.* **2006**, *8*, 5283−5285.
(4) (a) Our approach was inspired by an earlier partial synthesis; see: Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943−1946. (b) A further closely related synthesis of racemic clusianone has recently appeared; see: Nuhant, P.; David, M.; Pouplin, T.; Delpech, B.; Marazano, C. *Org. Lett.* **2007**, *9*, 287−289.
(5) McCandlish, L. E.; Hanson, J. C.; Stout, G. H. *Acta. Crystallogr.* **1976**, *B32*, 1793−1801.
(6) Brondz, I.; Greibrokk, T.; Groth, P.; Aason, A. J. *Acta. Chem. Scand.* **1983**, *A37*, 263−265.
(7) For other examples of bridgehead lithiation, see: Giblin, G. M. P.; Kirk, D. T.; Mitchell, L.; Simpkins, N. S. *Org. Lett.* **2003**, *5*, 1673−1675.
(8) For previous examples of chiral lithium amide kinetic resolution, see: (a) Kim, H.; Kawasaki, H.; Nakayima, M.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 6537− 6540. (b) Bambridge, K.; Clark, B. P.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2535−2541. (c) Coggins, P.; Simpkins, N. S. *Synlett* **1991**, *2*, 515−516. (d) Coggins, P.; Simpkins, N. S. *Synlett* **1992**, *2*, 313−314.

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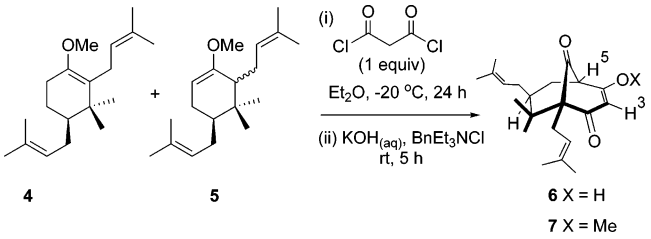
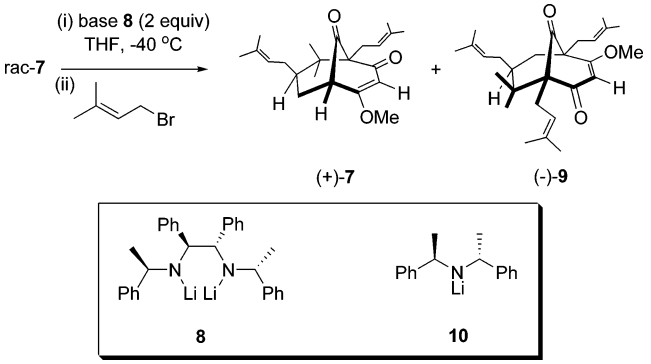
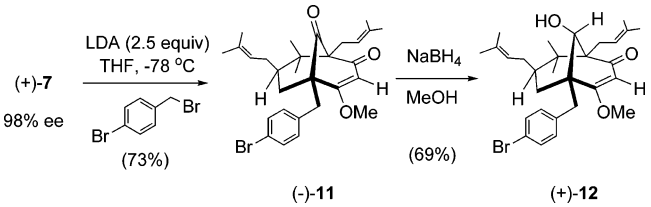
SCHEME 1



SCHEME 2



SCHEME 3



cally pure (ee >98%). Base **8**, in its bis-lithiated form, was found to be much more effective than the corresponding mono-lithiated diamine, which gave low ee and conversion, or the alternative base **10**, which gave good conversion but poorer selectivities—(−)-**7** of only about 50% ee was recovered at 70% conversion.

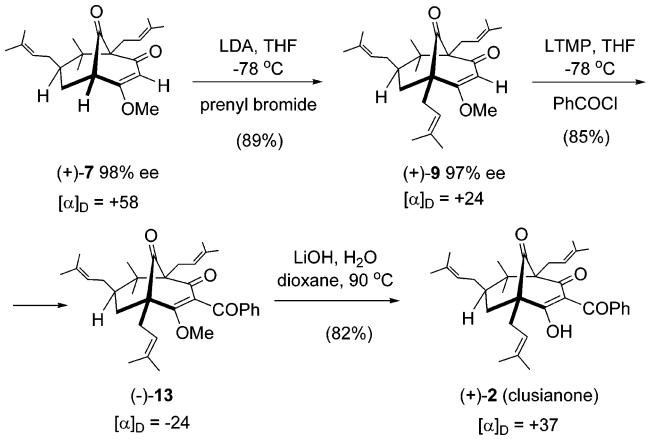
With supplies of enantiomerically enriched material in hand, we next sought to establish the absolute configuration of this material by X-ray crystallography. This was done by first effecting bridgehead benzylation, using *p*-bromobenzyl bromide, to give (−)-**11**, followed by reduction to give (+)-**12**, Scheme 3.

The latter compound provided suitable crystals for a crystal structure determination,[9] which enabled assignment of the absolute configuration of (+)-**12** and, hence, the other compounds shown in Schemes 2 and 3. In order to assign the configuration of clusianone we also converted a sample of (+)-**7** (>98% ee) into the natural product, as described in our previous paper, Scheme 4.

Conversion of (+)-**7** into clusianone establishes the absolute configuration of the (+)-isomer of this natural product, which has been isolated from *Clusia torresii.*[10]

One additional report from a Brazilian group describes the isolation of *O*-methylated clusianone (**13**), seemingly from

SCHEME 4



mixed floral extracts from a number of species.[11] In this case, **13** was described fully (matching our data) and had $[\alpha]_D$ +60.7 in chloroform (the same solvent that we used). This was unexpected, since our *O*-alkylated derivative showed a *negative* sign of rotation. Thus, in order to further support the correlation in Scheme 4 we took the *product* from Scheme 2, (−)-**9** (50% ee), and converted that material into (−)-clusianone via (+)-**13**, thus confirming the swap in signs of rotation between clusianone and the *O*-methylated derivative shown. The magnitude and signs of the rotations for the 50% ee series of compounds were consistent with those shown in Scheme 4, i.e., roughly half in magnitude and of the opposite sign.[12] From these results it appears that the clusianone isolated by the Brazilian group was (−)-clusianone. This aspect requires re-examination, but it therefore seems that clusianone should join the ranks of PPAPs available from Nature in either enantiomeric form.

The present work shows for the first time that kinetic resolution can be effected by bridgehead lithiation with a chiral base and demonstrates the utility of this approach in the assignment of absolute stereochemistry of PPAPs. We are presently examining samples of racemic and enantiomerically enriched clusianone in anticancer screens to determine if the activity of this compound resides in one enantiomer.

Experimental Section

Typical procedure for the kinetic resolution of (±)-**7** using chiral lithium amide **8**: Under an atmosphere of dry N_2, BuLi (1.6 M, 1.13 mL, 1.81 mmol, 4.0 equiv) was added to a solution of 1(*S*),2-(*S*)-diphenyl-*N*,*N*′-bis-[1(*R*)-phenylethyl]ethane-1,2-diamine (380 mg, 0.906 mmol, 2.0 equiv) in THF (6 mL) at −40 °C. The resulting pink solution was then stirred for 10 min at that temperature, and then stirred for 5 min at 0 °C, and transferred via canula to a solution of *rac*-**7** (156 mg, 0.453 mmol) in THF (8 mL) at −40 °C. Once the transfer was finished, prenyl bromide (314 μL, 2.72 mmol, 6 equiv) was added, and the resulting yellow solution was stirred at −40 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl and allowed to reach room temperature. The layers were separated and the aqueous phase was extracted using AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated

(9) Cambridge Crystallographic Data Centre, deposition no. CCDC 628369. The Flack parameter for this compound refined to −0.017(4) indicating that the absolute stereochemical assignment is as shown.

(10) Piccinelli, A. L.; Cuesta-Rubio, O.; Chica, M. B.; Mahmood, N.; Pagano, B.; Pavone, M.; Barone, V.; Rastrelli, L. *Tetrahedron* **2005**, *61*, 8206−8211.

(11) de Oliveira, C. M. A.; Porto, A. M.; Bittrich, V.; Vencato, I.; Marsaioli, A. J. *Tetrahedron Lett.* **1996**, *37*, 6427−6430.

(12) Rotation data, $[\alpha]_D$, for the 50% ee series, starting from (−)-**9**, were **9** (−7), **13** (+10), **2** (−22). Note that our rotation for ca. 98% ee clusianone was (reproducibly) lower than that reported in reference 10; see the Supporting Information for full details.

to an oil, which was purified by column chromatography (eluent petroleum ether/AcOEt 9/1) to give (−)-**9** (115 mg, 61%), and then (+)-**7**, containing 10% of product **9** (49 mg). Further purification by preparative thin-layer chromatography (eluent petroleum ether/AcOEt 9/1) provided (+)-**7** containing 2% of (−)-**9** (39 mg, 25%): R_f (**7**) = 0.31, R_f (**9**) = 0.37 (petroleum ether/AcOEt 8/2); (+)-**7**: $[\alpha]^{20}_D = +58$ (c = 1.2, $CHCl_3$); ee = 99% as determined by HPLC (chiral support CHIRALPAK AD-H, *n*-hexane/EtOH 99.5:0.5, 1 mL/min, retention times: 17 min (minor), 25 min (major). Spectral data identical with previously reported data for *rac*-**7** and *rac*-**9**.[3]

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Supporting Information Available: Complete experimental details and characterization data for new compounds, including HPLC for the ee determinations and X-ray data (displacement ellipsoid plot and CIF) for compound **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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