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A Total Synthesis of Tarchonanthuslactone Exploiting *N*-Pyrrole Carbinols as Efficient Stereocontrolling Elements

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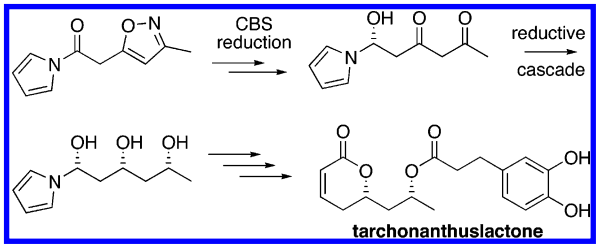
ABSTRACT



A short stereoselective total synthesis of the polyketide natural product, tarchonanthuslactone, has been achieved. The key sequence involves the first reported catalytic enantioselective reduction of an *N*-acyl pyrrole and subsequent use of this stereocenter in a diastereoselective reductive cascade. This proceeded with unprecedentedly high stereocontrol and offered an elegant method of generating the desired *syn* stereochemistry present in the final target in one step.

Tarchonanthuslactone **1**, a polyketide natural product, was first isolated from the leaves of *Tarchonanthus trilobus* in 1979.[1] It has been shown to lower the blood plasma glucose level in diabetic rats.[2] As part of its structural makeup it contains an α,*β*-unsaturated *δ*-lactone as well as two stereogenic acyloxy groups in a 1,3-*syn* relationship. The compound belongs to a group of biologically active natural products possessing these structural motifs and its relatives include passifloricin and the cryptocarya family.[3] As a consequence tarchonanthuslactone **1** and its cousins have been the subject of a number of total syntheses.[4]

The attractive structure and biological activity of tarchonanthuslactone made it an ideal target to develop new asymmetric synthetic methodology for its construction. More specifically, we believed this natural product offered us the perfect opportunity to develop a new method for the catalytic asymmetric construction, and subsequent application of the *N*-pyrrole carbinol motif in total synthesis.

Pyrrole carbinols are remarkably stable α-amino alcohols[5] that have been used as protecting groups for aldehydes,[6] isolated as intermediates in synthesis,[7] and, most recently,

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(2) Hsu, F. L.; Chen, Y. C.; Cheng, J. T. *Planta Med.* **2000**, *66*, 228.
(3) (a) Andrianaivoravelona, J. O.; Sahpaz, S.; Terreaux, C.; Hostettmann, K.; Stoeckli-Evans, H.; Rasolondramanitra, J. *Phytochemistry* **1999**, *52*, 265. (b) Echeverri, F.; Arango, V.; Quinones, W.; Torres, F.; Escobar, G.; Rosero, Y.; Archbold, R. *Phytochemistry* **2001**, *56*, 881. (c) Bouzbouz, S.; Cossy, J. *Org. Lett.* **2003**, *5*, 1995.
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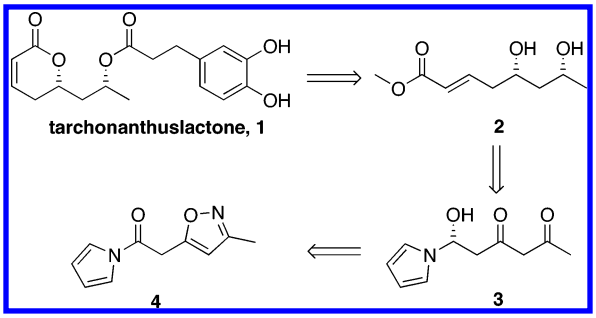
exploited as stereodirecting groups in diastereoselective transformations.[6b] The formation of pyrrole carbinols is possible by addition of metal pyrrolates to aldehydes or by reaction of *N*-acyl pyrroles with organometallic or hydride reagents.[5,6] To date, an efficient, catalytic enantioselective synthesis of this masked aldehyde equivalent remains elusive despite its potential value in asymmetric synthesis.

The reactivity and spectroscopic properties of *N*-acyl pyrroles (ν_{max}C=O 1713−1722 cm^{-1}) are similar to those of ketones.[5,8] This led us to believe that *N*-acyl pyrroles could be ideal substrates in catalytic asymmetric reduction reactions, where reagents such as acetophenone are reduced with high enantioselectivity.[9] Because such reactions are now commonplace in the literature and *N*-acyl pyrroles are readily prepared by a variety of methods[5,8] we believed this approach could provide powerful asymmetric access to the *N*-pyrrole carbinol motif.

We envisaged that the successful asymmetric generation of the pyrrole carbinol could be exploited as a key step in the total synthesis of tarchonanthuslactone **1**. Our synthetic strategy is shown in Scheme 1. Asymmetric reduction of

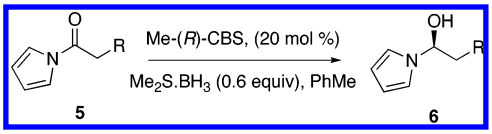
Scheme 1. Synthetic Plan for Tarchonanthuslactone Employing a Key *N*-Pyrrole Carbinol Intermediate



N-acyl pyrrole **4** possessing a masked 1,3-diketone functionality should provide pyrrole carbinol **3**, bearing a 1,3-related dione, after chemical manipulation. Exploitation of this newly formed stereocenter in a *syn*-selective reductive cascade should afford the *syn*,*syn*-1,3,5-triol and application of our deprotective olefination reaction[6] should furnish ester **2**. Subsequent pyranone formation and esterification of the remaining alcohol was expected to complete the total synthesis.

To assess the feasibility of this approach the reduction of *N*-propionoyl pyrrole **5a** was studied using commercially available Me-(*R*)-CBS reagent under standard conditions (Table 1).[10] Thus a solution of **5a** in toluene at 0 °C was treated with Me-(*R*)-CBS (20 mol %) and borane dimethyl

Table 1. Enantioselective CBS Reductions of *N*-Acyl Pyrroles



entry	R	temp/°C	ee/%[a]	product[b]	yield/%[c]
a	Me	10	90	**6a**	92
b	Me	0	89	**6a**	87
c	Me	−10	92	**6a**	89
d	H	0	82	**6b**	95
e	*n*-Pr	0	79	**6c**	85
f	OBn	0	98	**6d**	98

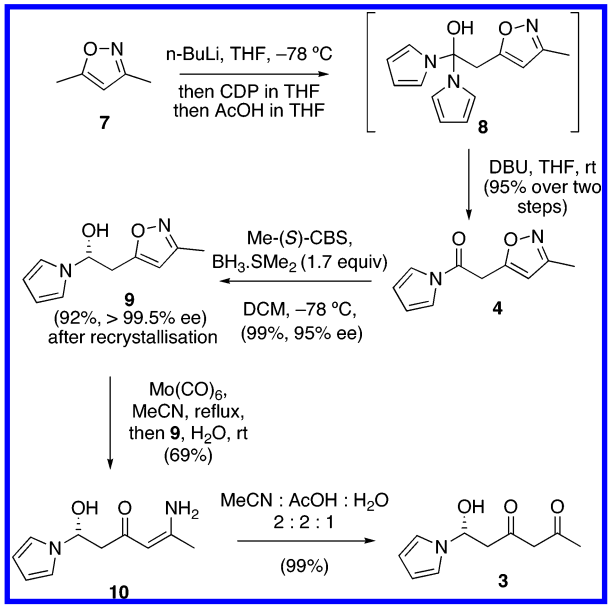
[a] Determined by chiral stationary phase HPLC. [b] The (*S*)-stereochemistry of **6a** was determined by Mosher ester analysis; **6b**−**d** were assigned by analogy. [c] Isolated yield after chromatography on silica gel.

sulfide complex. We were pleased to find the reaction was complete in 90 minutes, and after workup and purification, carbinol **6a** was isolated in an excellent yield (92%) and with 89% enantiomeric excess favoring the (*S*)-enantiomer (entry a).[11] Subsequent experiments demonstrated that cooling the reaction mixture had little effect on yield or enantioselectivity (entries b and c).

A substrate screen revealed that the enantioselective reduction was general. Thus at 0 °C, *N*-acetyl, *N*-pentoyl, and *N*-benzyloxyacetyl pyrroles were all reduced with good enantioselectivity and afforded the respective *N*-pyrrole carbinols in high yield (entries d−f).

Having established proof of principle, we turned our attention to the synthesis of tarchonanthuslactone. To avoid

Scheme 2. Highly Enantioselective Synthesis of Key *N*-Pyrrole Carbinol Intermediate **3**



chemoselectivity issues, we reasoned that the desired 1,3-diketone functionality would have to be masked during the

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(6) (a) Dixon, D. J.; Scott, M. S.; Luckhurst, C. A. *Synlett* **2003**, 2317. (b) Dixon, D. J.; Scott, M. S.; Luckhurst, C. A. *Synlett* **2005**, 2420. (c) See also: Cheeseman, M.; Feuillet, F. J. P.; Johnson, A. L.; Bull, S. D. *Chem. Commun.* **2005**, 2372.

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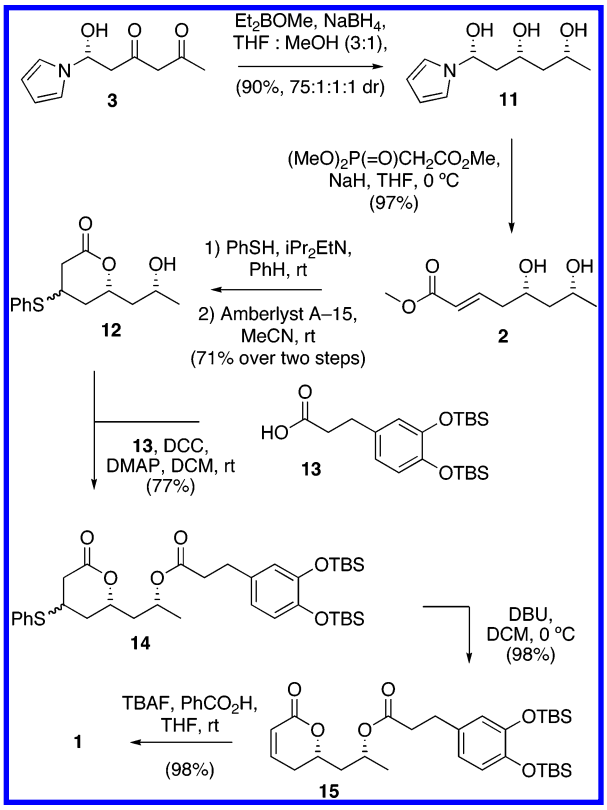
reduction of the *N*-acyl pyrrole functionality. An isoxazole was an attractive solution to this problem as the subsequent chemical manipulations required to liberate the 1,3-diketone were thought to be compatible with the pyrrole carbinol motif. Consequently, *N*-acyl pyrrole **4** was synthesized in high yield over two steps from 1,1′-carbonyldipyrrole (CDP).[5] Treatment of 2,5-dimethylisoxazole **7** with *n*-butyllithium at −78 °C followed by CDP gave **4** in multigram quantities after workup and treatment of the crude product with DBU.[5] To our initial disappointment, enantioselective reduction of **4** with Me-(*S*)-CBS reagent following the previously optimized conditions gave only a trace of product. This low reactivity was attributed to coordination of borane to the nitrogen of the isoxazole ring, and the low solubility of **4** in toluene.[12] To overcome this problem, the reaction was repeated in dichloromethane and an additional equivalent of borane dimethyl sulfide complex was employed. Gratifyingly this resulted in the formation of carbinol **9** in 98% yield and 95% ee on a multigram scale. Recrystallization gave **9** in 92% yield and greater than 99.5% ee.[13]

Reductive cleavage of the N−O bond with molybdenum hexacarbonyl in wet acetonitrile proceeded in good yield to give enamine **10**.[14] This was hydrolyzed to the diketone **3** in quantitative yield using aqueous acetic acid (Scheme 2).

Despite the potential synthetic value in the simultaneous creation of *syn*-1,3-related polyol sequences from parent hydroxy polyones, to the best of our knowledge there has been only one report of a moderately *syn*-selective reductive cascade to afford a *syn*,*syn*-1,3,5-triol.[15] This reaction employed a combination of titanium tetraisopropoxide and sodium borohydride on a 1-hydroxy-3,5-diketone starting material and gave at best 88:12 selectivity for the *syn*,*syn* diastereomer over all others combined.[15a]

In our case, treatment of **3** with diethylmethoxy borane and sodium borohydride in THF/methanol[16] at −78 °C smoothly reduced the hydroxydione **3** to the *syn*,*syn*-1,3,5-triol **11**, introducing all of the necessary stereocenters in our target, in excellent diastereoselectivity (75:1:1:1) and good yield (Scheme 3). This high diastereoselectivity is thought to arise through two, sequential diastereoselective keto group reductions, accelerated in each case by a boron chelate to the proximal *β*-carbinol. Thus, an initial axial attack of hydride on the 3-keto group, activated through a six-membered-ring boron chelate to the proximal *N*-pyrrole carbinol,

Scheme 3. Completion of the Total Synthesis of Tarchonanthuslactone via a Highly Diastereoselective Reductive Cascade on **3** to *syn*,*syn*-1,3,5-Triol **11**



lead to the formation of the first stereocenter with high stereocontrol. This was followed by a similar stereoselective process on the 5-keto group but controlled by a boron chelate to the newly formed 3-carbinol.[16] Pyrrole carbinol **11** was then subjected to our deprotective HWE conditions[6,17] to give the key α,*β*-unsaturated ester **2** in 97% yield as a single diastereomer after purification. Base-catalyzed conjugate addition of benzenethiol followed by acid-catalyzed lactonization gave alcohol **12**,[18] which was coupled with known acid **13**[4d] to afford ester **14**. Treatment of this ester with DBU in CH_2Cl_2 at 0 °C facilitated the elimination of benzene thiol to afford **15**. Finally, reaction of **15** with benzoic acid-buffered tetrabutylammonium fluoride (TBAF) afforded tarchonanthuslactone **1** in excellent yield (98%).[19]

In summary, an efficient total synthesis of tarchonanthuslactone has been achieved in 12 steps and 28% yield from 1,1′-carbonyldipyrrole. The stereocontrol in the sequence is the result of an enantioselective catalytic asymmetric reduction of an *N*-acyl pyrrole, followed by a highly diastereo-

(9) Cyclic *meso*-imides have been desymmetrized by reduction; see: (a) Dixon, R. A.; Jones, S. *Tetrahedron*: *Asymmetry* **2002**, *13*, 1115. (b) Ostendorf, M.; Romagnoli, R.; Cabeza Pereiro, I.; Roos, E. C.; Moolenaar, M. J.; Speckamp, W. N.; Hiemstra, H. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1773. (c) Romagnoli, R.; Roos, E. C.; Hiemstra, H.; Moolenaar, M. J.; Speckamp, W. N.; Kaptein, B.; Schoemaker, H. E. *Tetrahedron Lett.* **1994**, *35*, 1087.

(10) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987.

(11) The absolute stereochemistry was determined by Mosher's ester analysis (ref 6b) and is consistent with that predicted by the standard CBS model (ref 10).

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(13) Determined by chiral stationary phase HPLC.

(14) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1401.

(15) (a) Bonini, C.; Righi, G.; Rossi, L. *Tetrahedron* **1992**, *48*, 9801. For a moderately selective 1,3,5-*all-anti* reduction see: (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

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(17) For a similar transformation of *N*-hydroxyalkyl-5,5-dimethyloxazolidin-2-ones see: Bach, J.; Blachère, C.; Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Price, P. D.; Sanganee, H. J.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 2001 and references therein.

(18) Bernardi, R.; Ghiringhelli, D. *Gazz. Chim. It.* **1992**, *122*, 395.

(19) The spectroscopic data and specific rotation of the synthetic material are in good agreement with the literature values and confirmed the absolute and relative stereochemistry of the intermediates in the sequence. $[\alpha]^{25}_D$ −80.0 (*c* 0.4, $CHCl_3$) [lit.[4d] $[\alpha]_D$ −83.0 (*c* 0.4, $CHCl_3$)].

selective *syn*-selective reductive cascade. Further work in this and related areas will be reported in due course.

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Supporting Information Available: Full experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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