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Asymmetric Synthesis of a Fully Protected *ent*-Actinoidinic Acid

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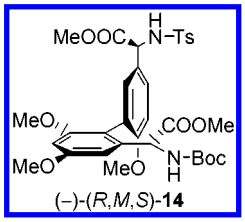
ABSTRACT



The asymmetric synthesis of a fully protected *ent*-actinoidinic acid derivative 14 is described. As key steps, an enantioselective deprotonation of an arenetricarbonylchromium(0) complex and a diastereoselective Suzuki coupling were applied. The asymmetric centers of the amino acid function were created via stereocontrolled Strecker reactions.

Planar chiral arenetricarbonylchromium(0) complexes have found, in recent years, a significant place in the range of organic synthetic protocols.[1] Several methods have been established to produce these complexes in enantiopure form, viz. resolution of a racemate,[2] diastereoselective complexation,[3] and diastereoselective[4] and enantioselective deprotonations.[5] Previously we have published our own investigations of arenetricarbonylchromium(0) complex deprotonation with the sparteine/BuLi base system,[6] and we now report the application of the methodology so developed to the synthesis of the chiral biaryl *ent*-actinoidinic acid.

Actinoidinic acid (**2**) is the biaryl di-aminoacid unit in vancomycin and related compounds such as teicoplanin. The vancomycin class of glycopeptide[7] antibiotics is widely used in the treatment of antibiotic-resistant bacteria and also for bacterial infections in patients allergic to the β-lactam-derived antibiotics. Recently total syntheses of vancomycin aglycone,[8] vancomycin (**1**) (Figure 1) itself,[9] and teicoplanin[10]

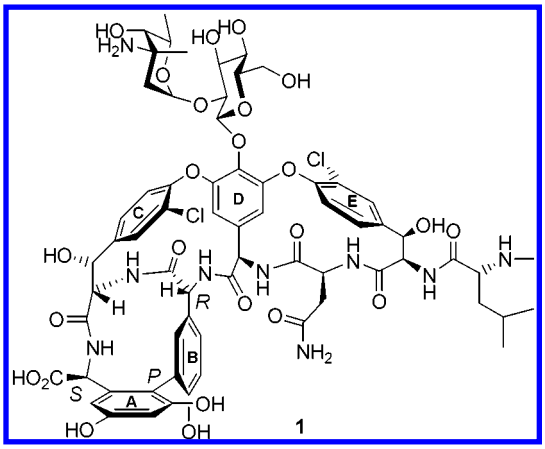


Figure 1. Vancomycin

have been published. Thus far, two groups have reported the synthesis of a protected actinoidinic acid,[11] and there is one approach for the asymmetric generation of the isolated

(1) Rose-Munch, F.; Rose E. *Curr. Org. Chem.* **1999**, *3*, 445−467.
(2) For examples, see: (a) Solladie-Cavallo, A. *Chiral Arene Chromium Carbonyl Complexes in Asymmetric Synthesis*; JAI Press: London, 1989; Vol. 1. (b) Bromley, L. A.; Davies S. G.; Goodfellow, C. L. *Tetrahedron: Asymmetry* **1991**, *2*, 139−156.
(3) For examples, see: (a) Alexakis, A.; Mangeney, P.; Marek, I.; Rose-Munch, F.; Rose, E.; Semra, A.; Robert, F. *J. Am. Chem. Soc.* **1992**, *114*, 8288−8290. (b) Uemura, M.; Minami, T.; Hirotsu, K.; Hayashi, Y. *J. Org. Chem.* **1989**, *54*, 469−477.
(4) For an example, see: Han, J. W.; Son, S. U.; Chung, Y. K. *J. Org. Chem.* **1997**, *62*, 8264−8267.

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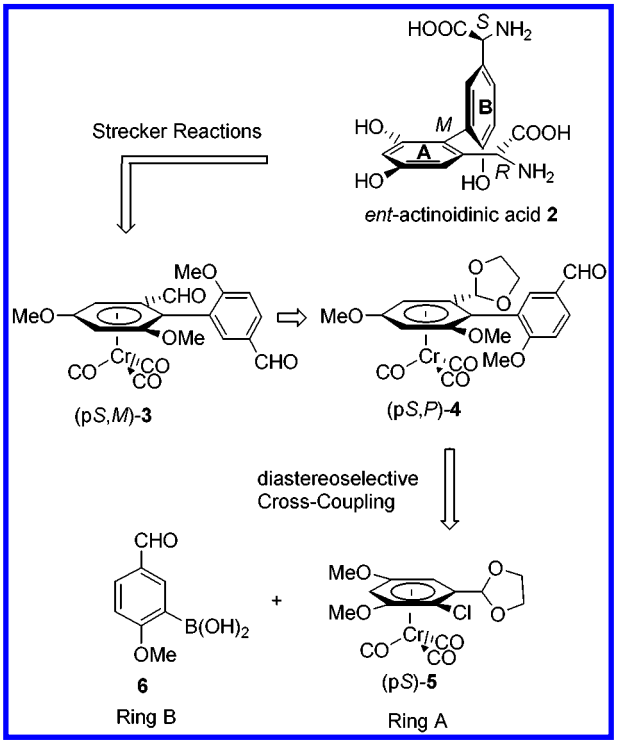
Scheme 1



biaryl system via an enantioselective cross-coupling reaction.[12] Furthermore, after submission of our work Uemura et al.[13] reported their preparation of the chiral AB-system of vancomycin.

Scheme 1 shows our retro synthetic approach to *ent*-actinoidinic acid. We considered that the amino acid stereocenters on the two aromatic rings of **2** would be formed using stereocontrolled Strecker reactions from the dialdehyde **3** or monoaldehyde **4**. The complex **4** would be formed directly through a diastereoselective coupling of ring A and B analogues. The planar chiral ring A analogue (p*S*)-**5** would be prepared by deprotonation of the precursor with the (−)-sparteine/*n*-BuLi system and quenching with hexachloroethane, while the ring B analogue **6** would be prepared according to literature procedures.[14]

Diastereoselective cross-coupling with arenetricarbonylchromium(0) complexes has been well studied by M. Uemura,[15] and our own investigations of cross-coupling with arenechromium complexes[16] confirmed that, in a Suzuki coupling with these complexes, the larger of the *ortho*-groups of the attacking areneboronic acid will be *syn* to the chromium fragment in the biaryl product as indicated in structure **4**. Because of the small size of the liberated formyl group, deprotection of the acetal function of **4**, even at room temperature, would result in rotation about the biaryl axis to the thermodynamically more stable diastereomer **3**.

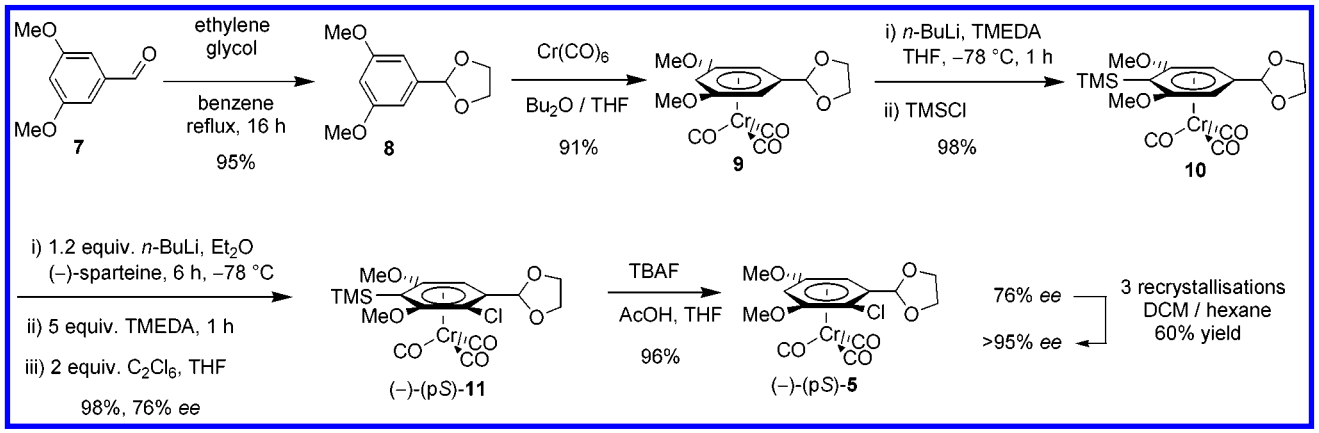
Given the widely different pharmacological effects of enantiomeric materials, it was of interest to synthesize *ent*-actinoidinic acid, but this stereochemistry was, in any case, dictated by the use of the commercially available (−)-sparteine and the stereoselectivity stemming from this as set out below. (+)-Sparteine is not currently commercially available but can be readily prepared from (−)-lupanine.[17]

The first target was enantiopure arenetricarbonylchromium(0) complex (p*S*)-**5** (Scheme 2). Commercially available aldehyde **7** was protected as the acetal **8** ($HOCH_2CH_2$-OH/benzene/Δ) in 95% yield. The arene ring of **8** was then complexed ($Cr(CO)_6$/Bu_2O/THF/Δ) to produce **9** in 91% yield. Lithiation of **9** occurs preferentially at C-4 of the aryl ring, so this position was blocked with a trimethylsilyl group (BuLi/TMEDA/TMSCl/−78 °C) to produce **10** in 98% yield.

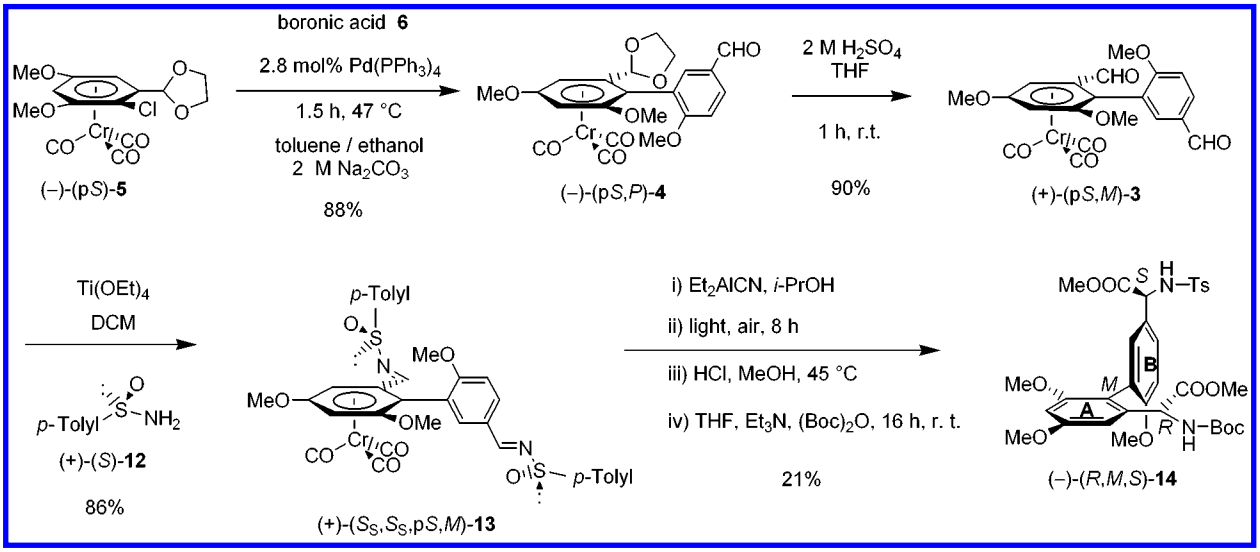
An enantioselective deprotonation of **10** with the (−)-sparteine/BuLi system removed the 2-*pro*-(*S*)-hydrogen, as previously described,[6] and 5 equiv of TMEDA was added to displace the bulky (−)-sparteine ligand prior to the addition of a hexachloroethane quench. The addition of TMEDA to the lithiated complex proved necessary in order to enhance the reactivity and to optimize the yield. Complex (p*S*)-**11** was so obtained in 98% yield with an ee of 76%. During the workup process the (−)-sparteine ligand was recovered in 95% yield after purification.

Desilylation of complex (p*S*)-**11** (TBAF/AcOH/THF) gave (p*S*)-**5** in 96% yield and 76% ee. It was possible to enhance the ee of complex (p*S*)-**5** by three crystallizations from DCM/hexane, which gave a 60% recovery in essentially enantiopure form (>95% ee). The process was monitored via

Scheme 2



Scheme 3



chiral HPLC (OD-H-column). Interestingly, it was the racemate that crystallized preferentially, leaving the (p*S*)-enantiomer in the mother liquor.

The enantiopure complex (p*S*)-**5** was then coupled with boronic acid **6**[14] to form (p*S*,*P*)-**4** in 88% yield (Scheme 3). An X-ray analysis of (p*S*,*P*)-**4** confirmed the absolute planar and axial stereochemistry. The acetal function was removed in 90% yield by subjection of (p*S*,*P*)-**4** to 2 M H_2SO_4 in THF (2:1) for 1 h as shown in Scheme 3. The methoxy group of ring B in the product (p*S*,*M*)-**3** was assigned as *anti* to the chromium fragment by the upfield shift of the ring B MeO-group resonance from 3.99 ppm for (p*S*,*P*)-**4** to 3.84 ppm for (+)-(p*S*,*M*)-**3** in the proton spectra and by analogy with the results of Uemura,[15] who demonstrated the free axial rotation when the aldehyde group on the complexed ring was regenerated.

The dialdehyde (p*S*,*M*)-**3** was then converted into the disulfinylimine complex **13** (86%) by treatment with the sulfinylamine (+)-(*S*)-**12** and titanium tetraethoxide[18] in readiness for a chiral Strecker reaction after Davis et al.[19] The Strecker reaction with Et_2AlCN gave the desired nitrile complex, but the complex proved to be very unstable. Therefore decomplexation with air and light was carried out immediately during which, interestingly, the sulfoxide group on ring B was oxidized to the sulfone, while the group on ring A remained untouched. Since it was inconvenient to purify the diamino dinitrile product, the crude compound was directly methanolysed to the methyl ester by treatment with HCl gas in methanol, a reaction that also removed the sulfoxide group on ring A. The crude product was then Boc-protected to give the fully protected *ent*-actinoidinic acid derivate **14** in a yield of 21% over the four steps (67% average per stage). An X-ray analysis confirmed the absolute stereochemistry.

As expected, the absolute axial stereochemistry remained (*M*), while on ring B an (*S*)-center was formed, as expected,

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from sulfoxide stereocontrol[19] of the Strecker reaction. In contrast, on ring A an (*R*)-center was formed because of the dominance, over sulfoxide control, of stereodirection by the tricarbonylchromium unit by which the attacking Et_2AlCN was only able to approach the imine carbon from the side opposite to the chromium fragment with the imino function in the preferred conformation *anti* to the adjacent aryl ring. This is well know for imine[20] and aldehyde[21] arenetricarbonylchromium(0) complexes.

The fortuitous formation of a sulfonyl group on the ring B amino function established differential protection of the amino functions in **14** and hence allows selective deprotection, a feature essential for further elaboration of the product. Although the sulfonyl group is generally a very stable protecting group for amines,[22] methods to remove the group under mild conditions include electrolysis at temperatures between 0 and 20 °C, an efficient method[23] that has been applied to amino acids and peptides without any epimerization of the α-center.[24]

In conclusion, a protected *ent*-actinoidinic acid was prepared via a short route involving three elements of stereocontrol: enantioselective deprotonation of an arenetricarbonylchromium(0) complex, a sulfinylimine-directed Strecker reaction, and a chromium-directed Strecker reaction. Full details and further developments will be published in a future paper.

Supporting Information Available: Detailed descriptions of experimental procedures and X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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