Natural Product Synthesis

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Nature-Inspired Stereospecific Total Synthesis of *P*-(+)-Dispegatrine and Four Other Monomeric *Sarpagine* Indole Alkaloids**

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The *sarpagine-macroline* group of indole alkaloids (biogenetically related to the *ajmaline*-related alkaloids)[1] consists of more than 150 members and is an important class of natural products with diverse biological activity.[2] Common to these three classes of alkaloids is the core cycloocta[*b*]indole framework **A** (Figure 1 a), which has recently been a subject of biology-oriented synthesis (BIOS),[3] the analogues of which are promising targets for developing a novel class of potent and selective Mycobacterium protein tyrosine phosphatase B (MptpB) inhibitors against *Mycobacterium tuberculosis*.[4] The *S* configuration at C6 and C10 and the β-ketoester moiety were key to the inhibitory activity.

Bisphenolic, bisquaternary indole alkaloids are very rare.[5] Of the 300 or so dimeric indole alkaloids isolated to date, the *sarpagine* alkaloid (+)-dispegatrine (**1**)[6] (Figure 1 b) and the *Coryanthé* alkaloid blumeanine[7] are the only two dimeric indoles belonging to this class. (+)-Dispegatrine (**1**) and the monomer (+)-spegatrine (**2**), isolated from the roots of *Rauwolfia verticillata* (Lour.) Baill var. *hainanensis Tsiang*,[6] are known to exhibit anti-hypertensive activity with the affinity of the dimer **1** to both the α1 and α2 adrenoreceptors at about an order of magnitude greater than that of the monomer **2**.[8] While the structure of **1** was assigned during isolation, the apparent axial chirality at the C9–C9′ biaryl axis was not determined. Although the isolation chemists attempted a semisynthesis of **1** through an oxidative phenolic coupling of **2** (Scheme 1 a), the yield of the process was very low (0.25 %).[6] A number of synthetically related monomeric alkaloids such as lochneram (**3**), 10-methoxyvellosimine (**4**), lochnerine (**5**), and sarpagine (**6**) have also been reported (Figure 1 b).[2c] The complex architecture combined with the promising bioactivity of **1**,[8] **2**,[8] and **5**[9] rendered them very attractive targets. Described herein is the first total synthesis of the *sarpagine* alkaloids **1**, **2**, and **4**–**6** in a stereospecific manner.

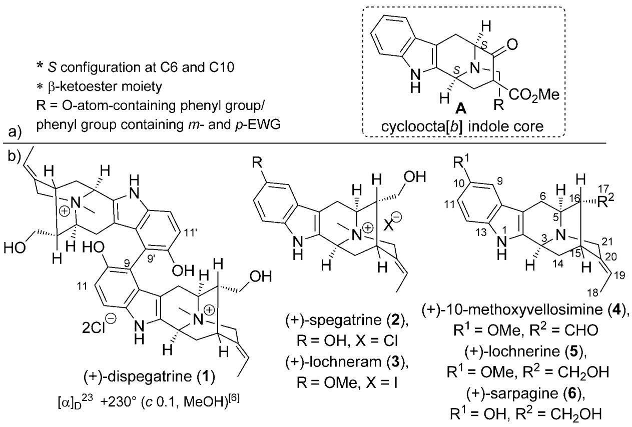
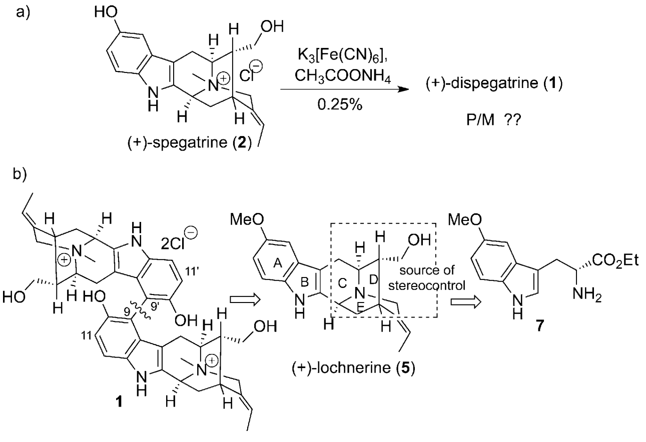


Figure 1. a) The cycloocta[*b*]indole core structure with promising inhibitory activity against MptpB.[4] b) Ring-A oxygenated *sarpagine* indole alkaloids **1**–**6**. EWG = electron-withdrawing group.



Scheme 1. a) Biomimetic semisynthesis of **1** by Yu and co-workers.[6] b) Doubly convergent retrosynthetic analysis of **1**. Proposed late-stage nonphenolic oxidative coupling (this work).

Direct biaryl bond formation can be classified into two types: a) the reductive metal-catalyzed coupling reaction (e.g Ullmann, Suzuki, Stille, C–H activation etc.) and b) the oxidative coupling reaction.[10] The regioselectivity of the reductive coupling is predetermined by the use of activated coupling partners (which may have to be synthesized separately). The oxidative coupling, in contrast, is a more direct and economical method for the synthesis of bi-

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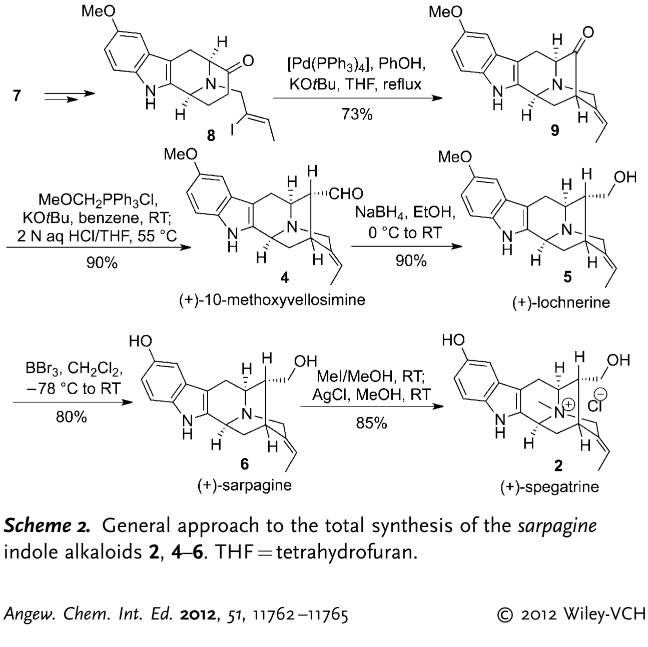
aryls.[10a,c,e,11] The lack of preactivation, however, could affect the regioselectivity of the process. For example, the presence of more than one reactive site in a phenolic substrate could lead to a mixture of regioisomers (through *ortho* and *para* coupling) and subsequent over oxidation to quinones, either from the coupled product or the original substrate, could lower the yield of the process. Atropselectivity in both cases is most commonly achieved by employing chiral catalysts[10–12] or, in a few cases, by taking advantage of either the existing chiral centers in the substrate[13] or by double diastereodifferentiation.[14]

The formation of the biaryl bond in a large number of bisphenolic natural products is assumed, and in some cases proven to be a result of an oxidative phenolic coupling.[15] The existence of **1** as a single atropodiastereomer both in nature and during semisynthesis suggests the simultaneous formation of the biaryl bond with internal asymmetric induction by the *sarpagine* framework of the monomer **2**. We based the retrosynthetic strategy on these reports (Scheme 1b). A potentially biomimetic intermolecular biaryl coupling could be employed to construct the C9–C9′ bond in **1**. As opposed to the extremely low-yielding phenolic coupling of **2**,[6] a Scholl-type oxidative coupling[16] of the methoxy analogue lochnerine (**5**) could be attempted to this end. We have been interested in the total synthesis of *sarpagine* indole alkaloids and a general route for the synthesis of related alkaloids using the asymmetric Pictet–Spengler reaction has been developed. Our strategy toward the synthesis of the monomers **2**–**6**, and in turn **1**, relied on this approach.[2a]

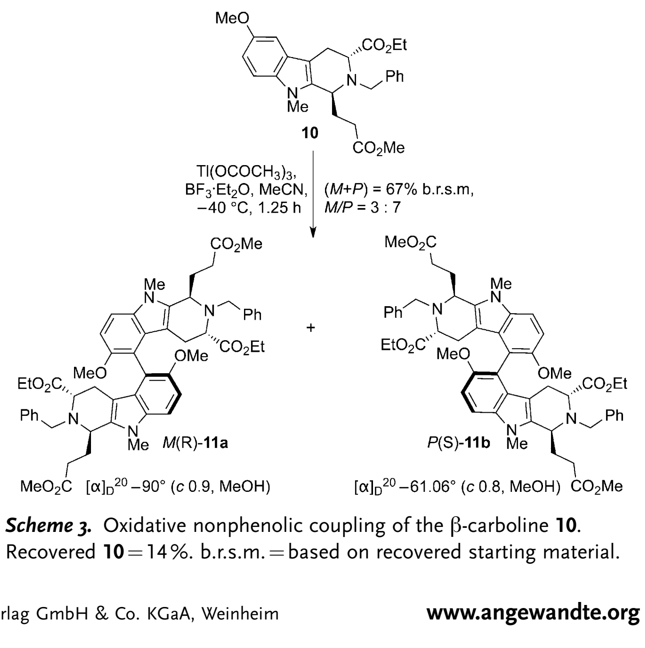
Analogous to the previous work of Zhao et al. in the N_a–Me series,[17] the 5-methoxy-N_aH-D(+)-tryptophan ethyl ester **7** was converted into the key tetracyclic core **8** in six steps by an asymmetric Pictet–Spengler approach (Scheme 2). Attempts to effect the key enolate-mediated palladium-catalyzed cyclization of the vinyl iodide **8** under the modified reaction conditions ([Pd$_2$(dba)$_3$]/DPEphos/*t*BuONa)[18] furnished the pentacyclic ketone **9** in lower yields (50 %), accompanied by the alkyne by-product (not shown). This problem was circumvented by subjecting **8** to the much milder conditions of Bonjoch et al.,[19] thus furnishing **9** in 73 % yield (Scheme 2). Wittig reaction of **9** and a subsequent hydrolysis/epimerization sequence provided the more stable α aldehyde in (+)-10-methoxyvellosimine (**4**). Reduction of the aldehyde **4** with $NaBH_4$/EtOH furnished (+)-lochnerine (**5**) in 90 % yield. Demethylation of **5** with BBr_3/CH_2Cl_2 furnished the phenolic monomer (+)-sarpagine (**6**) in 80 % yield. Subsequent N_b quaternization of **6** at room temperature with excess methyl iodide provided the N_b-methiodide salt, which upon stirring with silver chloride in ethanol[20] furnished (+)-spegatrine chloride (**2**). The spectral data of the synthetic **2** and **4**–**6** were in agreement with that reported for the natural products, and resulted in the first total synthesis of the alkaloids.[2c]

Intermolecular oxidative dimerizations of complex nonphenolic aryl substrates are very rare.[21] A majority of the documented examples constitute simpler aromatic systems or substrates with no competing reactive sites.[10e,22] To test the feasibility of such an intermolecular oxidative coupling on the electron-rich indole alkaloid **5** (with two possible reactive sites, C9 and C11), it was decided to first carry out a model reaction on a more robust substrate. The N_a-methyl β-carboline **10** (see Scheme 3 for structure), which was synthesized earlier,[17] was employed for this purpose. In the absence of a chiral catalyst, such a model reaction could also provide an insight into the possible substrate-dependent atropselectivity of the process.

Of the various combinations documented,[10e] the hypervalent-iodine(III)-mediated coupling conditions developed by Kita et al.[22b,23] and the thallium(III)-mediated conditions of Taylor et al.[22c,24] seemed best suited to the substrates under study here. As illustrated in Scheme 3, **10**, when subjected to iodine(III)- or thallium(III)-mediated oxidative coupling afforded a mixture of the atropodiastereomers **11a** and **11b** with complete regioselectivity. In general, the hypervalent-iodine-mediated oxidations [phenyliodine(III)bis(trifluoroacetate) (PIFA) or phenyliodine diacetate (PIDA) performed at −78 °C to 0 °C] generated a number of intensely colored baseline impurities. At best a combined



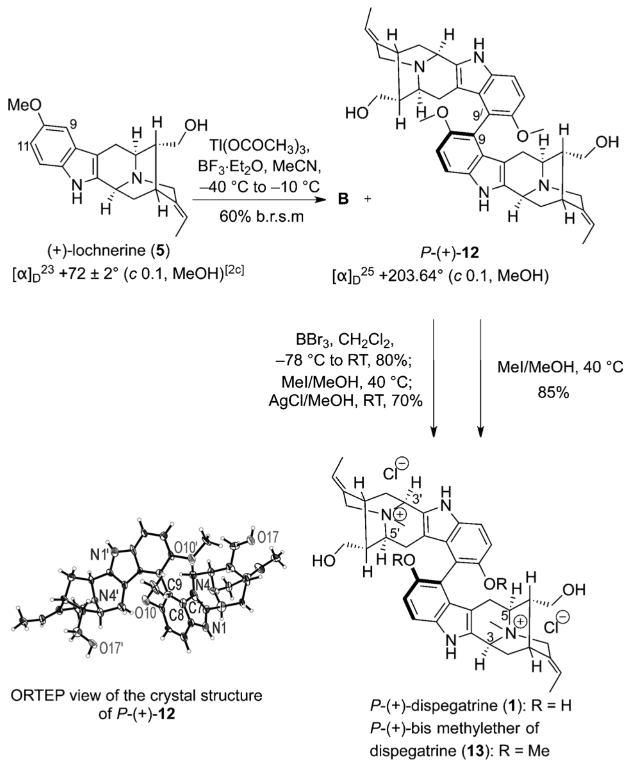
Scheme 2. General approach to the total synthesis of the *sarpagine* indole alkaloids **2**, **4**–**6**. THF = tetrahydrofuran.



Scheme 3. Oxidative nonphenolic coupling of the β-carboline **10**. Recovered **10** = 14 %. b.r.s.m. = based on recovered starting material.

yield of 30 % (**11a**/**11b** = 4:1) was obtained with a combination of PIFA (0.8 equiv) and BF$_3$·Et$_2$O (3 equiv) at −40 °C. However, with the thallium(III) salt [Tl(OCOCF$_3$)$_3$/Tl(OCOCH$_3$)$_3$] as the oxidant, the reaction was much cleaner with very little baseline material. Upon optimization, the milder thallium(III) acetate (0.7 equiv) with BF$_3$·Et$_2$O (3 equiv) at −40 °C provided a combined yield of 67 % (b.r.s.m.), in favor of **11b**. After chromatographic separation, the lower-R_f atropodiastereomer **11b** was recrystallized from EtOH and confirmed by X-ray analysis to have an axial chirality of *P*(S).[25] With the successful coupling of **10**, albeit in moderate yields, the oxidative dehydrodimerization of the indole **5** was next attempted.

As illustrated in Scheme 4, addition of solid **5** to a mixture of thallium(III) acetate (0.65 equiv) and BF$_3$·Et$_2$O (3.0 equiv) in acetonitrile at −40 °C to −10 °C afforded the C9–C9′ biaryl **12** as the sole atropodiastereomer in 60 % yield (b.r.s.m) with complete regioselectivity, which is in agreememt with the retrosynthetic analysis. Formation of a small amount of the the arylthallium adduct **B** (8 %) at C9, is in accordance with the mechanistic studies by Kochi et al.[26] The free indole N$_a$H, the highly basic N$_b$ atom, and the free OH group at C17 were unaffected. Attempts to achieve complete conversion of **5**, by increasing the equivalents of the thallium salt, led to increased formation of **B** and baseline impurities. Column chromatographic purification of the dimer **12**, followed by recrystallization from methanol provided white crystals for X-ray analysis, which established the axial configuration as *P*(S).[27] As anticipated, the rigid *sarpagine* framework and the existing stereogenic centers in **5** exerted complete atropselection in the key biaryl coupling step, thereby forming the single atropodiastereomer *P*-(+)-**12**. This would be in agreement with a potential biomimetic coupling in the plant since the other atropodiastereomer of **1** was not reported there or observed by us.



Scheme 4. Completion of the total synthesis of the *P* atropodiastereomer of (+)-dispegatrine (**1**). Recovered **5** = 14 %, **B** = the arylthallium adduct C$_{24}$H$_{29}$N$_2$O$_6$Tl (8 %). Thermal ellipsoids shown at 50 % probability.

With the axial chirality established in the key intermediate *P*-(+)-**12**, the total synthesis of **1** was completed in two steps as illustrated in Scheme 4. Demethylation of *P*-(+)-**12** was achieved with 11 equivalents of BBr$_3$/CH$_2$Cl$_2$ at −78 °C to furnish the bisphenol (not shown). N$_b$ quaternization of the highly polar bisphenol required heating of the reaction mixture in a sealed tube at 40 °C with a large excess of MeI to provide the methiodide salt. Additional treatment with AgCl/MeOH at room temperature completed the total synthesis of *P*-(+)-dispegatrine (**1**). Spectral analysis (^{1}H NMR spectroscopy and HRMS) of the synthetic **1** was in good agreement with that in the literature,[6] except the proton chemical shifts for H5,5′. To obtain better spectroscopic data, the bismethylether **13** was synthesized by carrying out the the N$_b$ quaternization of *P*-(+)-**12** with MeI/MeOH at either room temperature or 40 °C. Analogous to blumeanine (isolated as its diacetate),[7] chromatographic purification and isolation of the bisquaternary salt **13** proved to be much easier in comparison to **1**. The two-dimensional NMR correlation experiments (see the Supporting Information) on the dimer **13** established the position of the H3,3′ and H5,5′ protons. In the absence of an authentic sample[28] [for circular dichroism (CD) analysis or thin layer chromatography (TLC) comparison], it is impossible to unequivocally report that synthetic **1** is identical to the natural product even though the ^{1}H NMR data is in good agreement.[29] However the fact that the biomimetic coupling by Yu et al.[6] gave only the natural isomer and our oxidative coupling gave the *P* atropodiastereomer from similar scaffolds strongly suggests that they presumably are the same.

In summary, a general approach to the ring-A oxgenated N$_a$H *sarpagine* indole alkaloids has led to the first asymmetric total synthesis of the dimeric indole alkaloid *P*-(+)-dispegatrine (**1**) as well as the monomers **2**, **4–6**. The synthesis is notable especially for execution of the direct oxidative dimerization of (+)-lochnerine (**5**) in the presence of the free indole N$_a$H, the highly basic N$_b$ atom, and the C17 OH group. To the best of our knowledge, this is the first report of a direct intermolecular oxidative nonphenolic coupling of highly functionalized and sensitive substrates (**5** and **10**) and has expanded the scope of the thallium(III)-mediated oxidative coupling reaction in heteroaromatic biaryl synthesis. Additionally an indirect alternative to the less predictable phenolic coupling, especially in complex aryl substrates is presented.

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[1] M. Ruppert, X. Ma, J. Stöckigt, *Curr. Org. Chem.* **2005**, *9*, 1431–1444.

[2] For reviews on *sarpagine-macroline* indole alkaloids, see: a) C. R. Edwankar, R. V. Edwankar, S. K. Rallapalli, J. M. Cook, *Nat. Prod. Commun.* **2008**, *3*, 1839–1870; b) S. E. Lewis, *Tetrahedron* **2006**, *62*, 8655–8681; c) M. Lounasmaa, P. Hanhinen, M. Westersund in *The Alkaloids*, *Vol. 52* (Ed.: G. A. Cordell), Academic Press, San Diego, **1999**, pp. 103–195, and references therein.

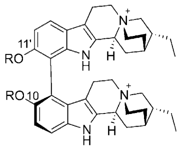
[3] S. Wetzel, R. S. Bon, K. Kumar, H. Waldmann, *Angew. Chem.* **2011**, *123*, 10990–11018; *Angew. Chem. Int. Ed.* **2011**, *50*, 10800–10826.

[4] a) A. Nören-Müller, J. I. Reis-Corrêa, H. Prinz, C. Rosenbaum, K. Saxena, H. Schwalbe, D. Vestweber, S. Schunk, O. Schwarz, H. Schiewe, H. Waldmann, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 10606–10611; b) A. Nören-Müller, W. Wilk, K. Saxena, H. Schwalbe, M. Kaiser, H. Waldmann, *Angew. Chem.* **2008**, *120*, 6061–6066; *Angew. Chem. Int. Ed.* **2008**, *47*, 5973–5977.

[5] a) T.-S. Kam, Y.-M. Choo in *The Alkaloids*, *Vol. 63* (Ed.: G. A. Cordell), Academic Press, San Diego, **2006**, pp. 182–345; b) G. A. Cordell, J. E. Saxton in *The Alkaloids*, *Vol. 20* (Eds.: R. H. F. Manske, R. G. A. Rodrigo), Academic Press, New York, **1981**, pp. 3–295.

[6] M. Lin, B. Yang, D.-Q. Yu, *Acta Pharm. Sin.* **1986**, *21*, 114–118.

[7] D. Arbain, D. Firmansyah, D. M. V. Sargent, B. W. Skelton, A. H. White, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2537–2540.



R = H, *P*-(−)-blumeanine
R = Ac, *P*-(−)-blumeanine acetate

[8] Y. Feng, H. Gao, G. Zeng, *Acta Pharm. Sin.* **1986**, *21*, 1–6.

[9] a) K. Zaima, I. Koga, N. Iwasawa, T. Hosoya, Y. Hirasawa, T. Kaneda, I. S. Ismail, N. H. Lajis, H. Morita, *J. Nat. Med.* **2012**, DOI: 10.1007/s11418-012-0638-y; b) G. H. Svoboda, D. A. Blake in *The Catharanthus Alkaloids* (Eds.: W. I. Taylor, N. R. Farnsworth), Marcel Dekker, New York, **1974**, p. 45, and references therein.

[10] For reviews on biaryl synthesis, see: a) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563–639; b) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; c) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518–5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427; d) T. M. Wallace, *Org. Biomol. Chem.* **2006**, *4*, 3197–3210; e) I. Cepanec, *Synthesis of Biaryls*, 1st ed, Elsevier, San Diego, **2004**; f) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M, Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1470.

[11] a) J. A. Ashenhurst, *Chem. Soc. Rev.* **2010**, *39*, 540–548; b) M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193–3207.

[12] a) A. N. Cammidge, K. V. L. Crépy, *Tetrahedron* **2004**, *60*, 4377–4386; b) J. Yin, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12051–12052.

[13] S. Huang, T. B. Petersen, B. H. Lipshutz, *J. Am. Chem. Soc.* **2010**, *132*, 14021–14023.

[14] a) Y. S. Park, C. I. Grove, M. Gonzalez-Lopez, S. Urgaonkar, J. C. Fettinger, J. T. Shaw, *Angew. Chem.* **2011**, *123*, 3814–3817; *Angew. Chem. Int. Ed.* **2011**, *50*, 3730–3733; b) G. Bringmann, A. Hamm, M. Schraut, *Org. Lett.* **2003**, *5*, 2805–2808.

[15] G. M. Keserú, M. Nógrádi in *Studies in Natural Products Chemistry*, *Vol. 20* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1998**, pp. 263–322.

[16] a) P. Kovacic, M. B. Jones, *Chem. Rev.* **1987**, *87*, 357–379; b) R. Scholl, C. Seer, *Justus Liebigs Ann. Chem.* **1912**, *394*, 111–177; c) R. Scholl, J. Mansfeld, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1734–1746.

[17] S. Zhao, X. Liao, T. Wang, J. Flippen-Anderson, J. M. Cook, *J. Org. Chem.* **2003**, *68*, 6279–6295.

[18] X. Liao, H. Zhou, J. Yu, J. M. Cook, *J. Org. Chem.* **2006**, *71*, 8884–8890.

[19] D. Solé, D. X. Urbaneja, J. Bonjoch, *Adv. Synth. Catal.* **2004**, *346*, 1646–1650.

[20] N. Yamazaki, W. Dokoshi, C. Kibayashi, *Org. Lett.* **2001**, *3*, 193–196.

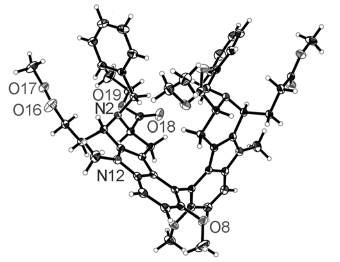
[21] G. Bringmann, S. Tasler, *Tetrahedron* **2001**, *57*, 331–343.

[22] a) P. A. Keller, N. R. Yepuri, M. J. Kelso, M. Mariani, B. W. Skelton, A. H. White, *Tetrahedron* **2008**, *64*, 7787–7795; b) H. Tohma, H. Morioka, S. Takizawa, M. Arisawa, Y. Kita, *Tetrahedron* **2001**, *57*, 345–352; c) A. McKillop, A. G. Turell, D. W. Young, E. C. Taylor, *J. Am. Chem. Soc.* **1980**, *102*, 6504–6512.

[23] a) T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, H. Fujioka, Y. Kita, *Tetrahedron* **2009**, *65*, 10797–10815; b) T. Takada, M. Arisawa, M. Gyoten, R. Hamada, H. Tohma, Y. Kita, *J. Org. Chem.* **1998**, *63*, 7698–7706.

[24] A. McKillop, E. C. Taylor in *Advances in Organometallic Chemistry*, *Vol. 11* (Eds.: F. G. A. Stone, R. West), Academic Press, New York, **1973**, pp. 147–206.

[25] ORTEP view of the crystal structure of *P*(S)-**11b**. Thermal ellipsoids shown at 50% probability.



CCDC 893770 [*P*(S)-**11b**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[26] W. Lau, J. K. Kochi, *J. Am. Chem. Soc.* **1984**, *106*, 7100–7112.

[27] CCDC 893771 [*P*-(+)-**12**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[28] A request was made for an authentic sample of **1**.

[29] For examples of homo- and hetero-atropodiastereomeric natural products that have almost identical ^{1}H and ^{13}C NMR spectra, see: a) Y. Hirasawa, M. Hara, A. E. Nugroho, M. Sugai, K. Zaima, N. Kawahara, Y. Goda, K. Awang, A. H. A. Hadi, M. H. Litaudon, *J. Org. Chem.* **2010**, *75*, 4218–4223; b) K. Tatsuta, T. Yamazaki, T. Mase, T. Yoshimoto, *Tetrahedron Lett.* **1998**, *39*, 1771–1772; c) Y. Fukuyama, Y. Asakawa, *J. Chem. Soc. Perkin Trans. 1* **1991**, 2737–2741.