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Gram-Scale Synthesis of the (–)-Sparteine Surrogate and (–)-Sparteine

James D. Firth,^[a] Steven J. Canipa,^[a] Leigh Ferris^[b] and Peter O'Brien^{*[a]}

Abstract: An 8-step, gram-scale synthesis of the (–)-sparteine surrogate (22% yield, with just 3 chromatographic purifications) and a 10-step, gram-scale synthesis of (–)-sparteine (31% yield) are reported. Both syntheses proceed with complete diastereocontrol and allow access to either antipode. Since the syntheses do not rely on natural product extraction, our work addresses long-term supply issues relating to these widely used chiral ligands.

The natural product sparteine and its structurally related cousin, the sparteine surrogate (Scheme 1) developed in our laboratory,^[1] are widely used chiral ligands in asymmetric synthesis. In particular, these diamines are the “go-to” chiral ligands for organolithium bases such as *s*-BuLi^[2] for use in reactions pioneered in the 1990s by Hoppe^[3] and Beak.^[4] The more recent work from the Aggarwal group on programmable assembly-line synthesis^[5] using chiral boron reagents (generated from *s*-BuLi/chiral diamine-mediated asymmetric lithiations) has significantly expanded the synthetic potential offered by sparteine and the sparteine surrogate.

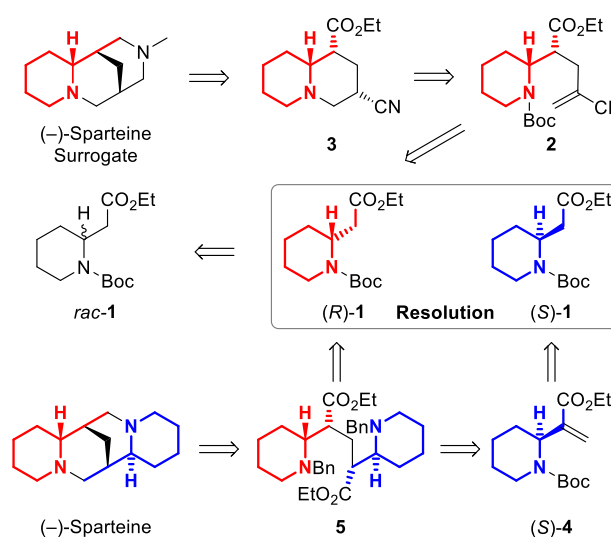
Both (–)- and (+)-sparteine are naturally occurring^[6] and are thus commercially available, although the availability of each antipode has varied over the last 20 years!^[7] They can also be obtained from the alkaloid lupanine *via* a resolution procedure,^[8] recently patented by Maulide *et al.*^[9] In contrast, only the (+)-sparteine surrogate is commercially available but, due to its high price, it is best obtained by our group's gram-scale synthesis from the natural product (–)-cytisine.^[10] The main issue with all of these sources of sparteine/sparteine surrogate is that they rely on natural product extractions and this can lead to supply issues (as observed for (–)- and (+)-sparteine over the last few years).^[7] Indeed, during the development of the hepatitis C drug, Telaprevir, researchers at Vertex rejected a process-scale route that used the (+)-sparteine surrogate since “inquiries about long-term, high-volume supply of (–)-cytisine had been met with concerns about production variability, due mainly to reliance on (–)-cytisine isolation from natural sources”.^[11]

The lack of adoption of the (+)-sparteine surrogate by process chemists at Vertex re-ignited our desire to develop a new synthesis of the sparteine surrogate that would allow access to both antipodes on a gram-scale. Furthermore, the sparteine surrogate has a much broader synthetic scope than sparteine due

to a greatly enhanced reactivity of the *s*-BuLi/sparteine surrogate complex. For example, the high reactivity of the *s*-BuLi/sparteine surrogate complex was required for one of the steps in Aggarwal's recently completed total synthesis of (–)-stemaphylline^[12] and was crucial for the high yielding lithiation-trapping of *N*-Boc piperidine.^[13]

Over the years, our group^[10,14] and others^[15] have explored synthetic approaches to enantiopure (+)- and (–)-sparteine surrogate. However, all approaches are either inconveniently long, lack diastereo- and/or regioselectivity, only allow access to one enantiomer and/or proceed with overall low yields. These limitations have thus far precluded the synthesis of enantiopure (+)- and (–)-sparteine surrogate on a gram-scale and addressing this is the primary topic of this paper. In addition, in designing our new approach to the sparteine surrogate, we also recognized that it could also be adapted to deliver a new resolution-reconnection strategy for the gram-scale synthesis of (–)-sparteine. Despite numerous syntheses of racemic sparteine over 65 years,^[16] there are only two enantioselective syntheses (by Aubé^[17] and our group^[18]) which delivered ~50 mg quantities of (+)- or (–)-sparteine over long or low yielding approaches.

Our retrosynthetic analyses and design concepts are shown in Scheme 1. We envisaged that the (–)-sparteine surrogate would be derived from quinolizidine **3** *via* reduction and *N*-methylation; the quinolizidine ring would be constructed from **2** by deprotection and conjugate addition of the amine to the α,β -unsaturated nitrile, where we predicted that axial protonation of the intermediate nitrile anion would set the required *cis* relative stereochemistry for bispidine formation. Diastereoselective alkylation (precedented with other electrophiles^[19]) of piperidine (*R*)-**1** obtained by enzymatic resolution^[20] would deliver nitrile **2**.



Scheme 1. Retrosynthetic analysis of (–)-sparteine surrogate and (–)-sparteine.

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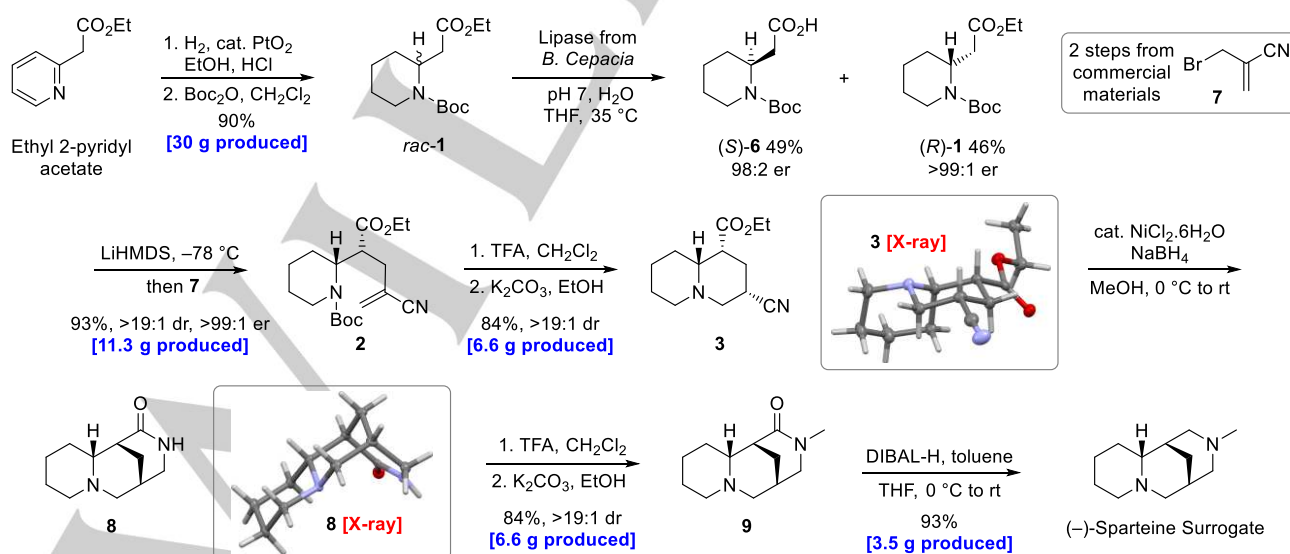
For (–)-sparteine, we realized that the two resolved enantiomers of **1** could, if they were recombined, make up the entire (–)-sparteine skeleton except for the bridging methylene group. Therefore, separation and recombination of **1**, with methylene incorporation, would lead to a highly connective synthesis of enantiopure (–)-sparteine from a simple racemic starting material that had been resolved into its two enantiomers. We anticipated that this resolution-recombination strategy should improve the efficiency of our earlier (–)-sparteine synthesis which proceeded *via* the same strategy.^[18] In our planned route, (–)-sparteine would be derived from bis-ester **5** by *N*-deprotection, amide formation and reduction. A Michael reaction of the enolate of (*R*)-**1** and α,β -unsaturated ester (*S*)-**4** (itself crafted from (*S*)-**1** with the extra methylene unit) would give bis-ester **5**. The relative stereochemistry in **5** would be assured if the reaction (enolate Michael addition and enolate protonation) followed the same diastereoselectivity as in enolate alkylations.^[18,19]

The optimized synthesis of the (–)-sparteine surrogate is shown in Scheme 2. Using a known method,^[14b,c] racemic ester *rac*-**1** was synthesised by pyridine hydrogenation and Boc protection in 90% yield over 2 steps on a 30 g scale (no chromatography, see SI for details). Using conditions optimized from a related literature protocol,^[20] treatment of ~10 g batches of racemic **1** with lipase from *Burkholderia cepacia*, in a mixture of THF and phosphate buffer (pH 7.0) at 35 °C, resulted in the isolation (after simple filtration and aqueous work-up, no chromatography) of acid (*S*)-**6** (49%, 98:2 er) and enantiopure ester (*R*)-**1** (46%, >99:1 er).

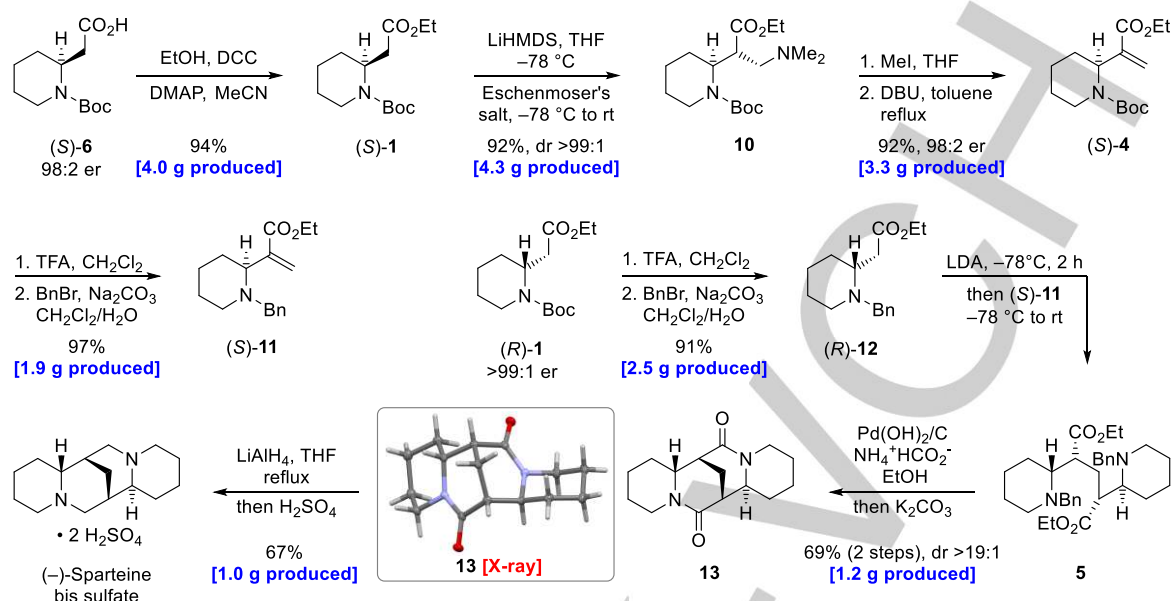
With significant quantities of (*R*)-**1** in hand, attention turned to construction of the full carbon skeleton of the (–)-sparteine surrogate. We initially explored the use of a bis-ester analogue of **3** but the end-game was less efficient than that *via* **3** (see SI for details). Installation of the acrylonitrile and the accompanying stereocentre was achieved through alkylation of the lithium enolate derived from (*R*)-**1** with 2-bromomethylacrylonitrile **7**,^[15c] giving **2** in 93% yield (after chromatography) as a single diastereomer, without any reduction in er. At this stage, the

relative stereochemistry of **2** was assigned based on Knight's precedent.^[19] Subsequent Boc cleavage followed by an intramolecular conjugate addition reaction between the resulting amine and α,β -unsaturated nitrile gave key quinolizidine **3** in 84% yield (after chromatography) as a single diastereomer. The relative stereochemistry was identified by X-ray crystallography.^[21] Interestingly, quinolizidine **3** adopts a *cis*-decalin conformation with the ester and nitrile substituents adopting equatorial positions. Assuming that the nitrile anion formed after conjugate addition adopts a conformation similar to this X-ray structure, then axial protonation on the less sterically hindered top face would account for the observed diastereoselectivity.

With all three stereocentres set, we then formed the bispidine framework of the (–)-sparteine surrogate. Selective reduction of the nitrile of quinolizidine **3**, with *in situ* generated nickel boride, and concomitant lactamisation gave **8**.^[15c] The structure of **8** was confirmed by single crystal X-ray diffraction^[21] and clearly showed the *trans*-decalin framework. Thus, ring flipping *via* nitrogen inversion can allow the aminomethyl and ester groups to adopt the required axial positions for cyclisation (compare with the X-ray structure of **3**). Next, methylation of lactam **8** with NaH and MeI proceeded well, giving **9** in 72% (after chromatography) over 2 steps and completing the skeleton of the (–)-sparteine surrogate. Reduction of the lactam **9** initially proved problematic, with the use of LiAlH₄^[14a] or borane^[22] giving complex mixtures. Gratifyingly, the use of DIBAL-H resulted in clean reduction of the lactam, giving 3.5 g of the (–)-sparteine surrogate in 93% yield after distillation. The optical rotation ($[\alpha]_D -29.2$ (c 1.0, EtOH)) mirrored that of semi-synthetic (+)-sparteine surrogate ($[\alpha]_D +29.7$ (c 1.1, EtOH)^[10]). Of note, this gram-scale, fully diastereocontrolled synthesis proceeded in 22% overall yield over 8 steps^[23] from commercially available materials, with only 3 chromatographic separations and one distillation utilised.



Scheme 2. Multigram synthesis of the (–)-sparteine surrogate.



Scheme 3. Total synthesis of (–)-sparteine.

We also used piperidines (S)-6 and (R)-1 in a total synthesis of (–)-sparteine (Scheme 3); in this case, all intermediates except **5** were purified by chromatography. Acid (S)-6 was re-esterified under Steglich conditions, giving (S)-1 in 94% yield. Next, installation of the requisite methylene group was achieved through the use of Eschenmoser's salt. Enolization with LiHMDS followed by trapping gave amine **10** as a single diastereomer in 92% yield. The relative stereochemistry in **10** has not been proven but is likely to be as shown based on related alkylations (*vide infra*). Methylation and DBU-mediated elimination gave α,β -unsaturated ester (S)-4 in 92% yield, with no racemization. Disappointingly, all attempts to add an enolate derived from Boc-protected (R)-1 to (S)-4 resulted in the generation of complex mixtures of products. Therefore, we resorted to switching the protecting groups. Benzyl protected piperidines (S)-11 and (R)-12 were obtained in 97% and 91% yields from (S)-1 and (R)-1 respectively. Gratifyingly, using conditions based on a related example from the literature,^[22] treatment of (R)-12 with LDA at –78 °C before addition of α,β -unsaturated ester (S)-11 led to a successful Michael addition to give **5**, with complete control over the two newly-formed stereocentres. The stereoselectivity presumably arises due to the Michael addition and protonation of the intermediate enolate following the same sense of induction as previously reported enolate alkylations.^[18,19] Debenzylation of **13** under transfer hydrogenolysis conditions, was followed by *in situ* bis-lactamisation (upon addition of K_2CO_3), giving lactam **13** as a single diastereomer in 69% over 2 steps, on a gram-scale. The relative stereochemistry was confirmed by single crystal X-ray diffraction.^[21] Amide reduction completed the synthesis of (–)-sparteine, which was isolated as the bisulfate salt,^[24] after recrystallization, in 67% yield.^[25] The optical rotation (of the free base, $[\alpha]_D -20.4$ (c 1.0, EtOH)(lit.,^[17] ($[\alpha]_D -20.7$ (c 1.8, EtOH)) confirmed that (–)-sparteine had been synthesised. Overall, this

diastereocontrolled synthesis of (–)-sparteine was completed in 10 steps (longest linear sequence^[23]) in 31% yield.

In summary, we have presented a unified strategy for the gram-scale synthesis of the (–)-sparteine surrogate and the lupin alkaloid (–)-sparteine, with full control over relative and absolute stereochemistry. The modular nature of the routes facilitates the synthesis of either antipode of the sparteine surrogate and sparteine and thus addresses any long-term supply issues relating to these synthetically useful chiral ligands.

Acknowledgements

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Keywords: Total synthesis • Alkaloids • Asymmetric synthesis • N-ligands • Kinetic resolution

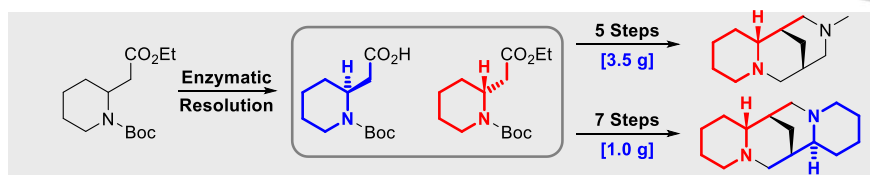
- [1] (a) M. J. Dearden, C. R. Firkin, J.-P. R. Hermet, P. O'Brien, *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871; (b) P. O'Brien, *Chem. Commun.* **2008**, 655–667.
- [2] (a) D. Hoppe, T. Hense, *Angew. Chem. Int. Ed.* **1997**, *36*, 2282–2316; *Angew. Chem.* **1997**, *109*, 2376–2410; (b) M. Breuning, M. Steiner, *Synthesis* **2008**, 2841–2867; (c) J.-C. Kizirian, *Chem. Rev.* **2008**, *108*, 140–205; (d) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092–10142.
- [3] D. Hoppe, F. Hintze, P. Tebben, *Angew. Chem. Int. Ed.* **1990**, *29*, 1422–1424; *Angew. Chem.* **1990**, *102*, 1457–1459.
- [4] S. T. Kerrick, P. Beak, *J. Am. Chem. Soc.* **1991**, *113*, 9708–9710.
- [5] (a) M. Burns, S. Essafi, J. R. Bame, S. P. Bull, M. P. Webster, S. Balieu, J. W. Dale, C. P. Butts, J. N. Harvey, V. K. Aggarwal, *Nature* **2014**, *513*, 183–188; (b) S. Balieu, G. E. Hallett, M. Burns, T. Bootwicha, J. Studley, V. K. Aggarwal, *J. Am. Chem. Soc.* **2015**, *137*, 4398–4403; (c) A. Noble,

- S. Roesner, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2016**, *55*, 15920–15924; *Angew. Chem.* **2016**, *128*, 16152–16156; (d) T. Bootwicha, J. M. Feilner, E. L. Myers, V. K. Aggarwal, *Nat. Chem.* **2017**, *9*, 896–902.
- [6] P. M. Dewick, *Medicinal Natural Products: A Biosynthetic Approach*, Wiley, Chichester, **2009**, p. 311.
- [7] S. K. Ritter, *Chem. Eng. News* **2017**, *95*, 18–20.
- [8] A. K. Przybył, M. Kubicki, *Tetrahedron* **2011**, *67*, 7787–7793.
- [9] N. Maulide, B. Peng, A. C. A. Mateus, F. R. F. Machado (Studiengesellschaft Kohle mbH, Universidade de Lisboa), EP2808326A1, **2014**.
- [10] A. J. Dixon, M. J. McGrath, P. O'Brien, *Org. Synth.*, **2006**, *83*, 141–154.
- [11] G. J. Tanoury, M. Chen, Y. Dong, R. Forslund, V. Jurkauskas, A. D. Jones, D. Belmont, *Org. Process Res. Dev.* **2014**, *18*, 1234–1244.
- [12] A. Varela, L. K. B. Garve, D. Leonori, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2017**, *56*, 2127–2131; *Angew. Chem.* **2017**, *129*, 2159–2163.
- [13] D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham, A. Sanderson, *J. Am. Chem. Soc.* **2010**, *132*, 7260–7261.
- [14] (a) J.-P. R. Hermet, A. Viterisi, J. M. Wright, M. J. McGrath, P. O'Brien, A. C. Whitwood, J. Gilday, *Org. Biomol. Chem.* **2007**, *5*, 3614–3622; (b) J. D. Firth, P. O'Brien, L. Ferris, *Org. Biomol. Chem.* **2014**, *12*, 9357–9365; (c) J.-P. R. Hermet, D. W. Porter, M. J. Dearden, J. R. Harrison, T. Koplin, P. O'Brien, J. Parmene, V. Tyurin, A. C. Whitwood, J. Gilday, N. M. Smith, *Org. Biomol. Chem.* **2003**, *1*, 3977–3988.
- [15] (a) B. Danieli, G. Lesma, D. Passarella, P. Piacenti, A. Sacchetti, A. Silvani, A. Virdis, *Tetrahedron Lett.* **2002**, *43*, 7155–7158; (b) B. Danieli, G. Lesma, D. Passarella, A. Sacchetti, A. Silvani, *Tetrahedron Lett.* **2005**, *46*, 7121–7123; (c) D. Scharnagel, A. Müller, F. Prause, M. Eck, J. Goller, W. Milius, M. Breuning, *Chem. Eur. J.* **2015**, *21*, 12488–12500.
- [16] (a) G. R. Clemons, R. Raper, W. S. Short, *J. Chem. Soc.* **1949**, 663–665; (b) N. J. Leonard, R. E. Beyler, *J. Am. Chem. Soc.* **1950**, *72*, 1316–1323; (c) E. F. L. J. Anet, G. K. Hughes, E. Richie, *Aust. J. Sci. Res.*, **1950**, 635; (d) E. E. van Tamelen, R. L. Foltz, *J. Am. Chem. Soc.* **1960**, *82*, 2400; (e) E. E. Van Tamelen, R. L. Foltz, *J. Am. Chem. Soc.* **1969**, *91*, 7372–7377; (f) F. Bohlmann, E. Winterfeldt, U. Fries, *Chem. Ber.* **1963**, *96*, 2251–2253; (g) F. Bohlmann, H.-J. Müller, D. Schumann, *Chem. Ber.* **1973**, *106*, 3026–3034; (h) N. Takatsu, M. Noguchi, S. Ohmiya, H. Otomasu, *Chem. Pharm. Bull.* **1987**, *35*, 4990–4992; (i) M. J. Wanner, G.-J. Koomen, *J. Org. Chem.* **1996**, *61*, 5581–5586; (j) T. Buttler, I. Fleming, *Chem. Commun.* **2004**, 2404–2405; (k) T. Buttler, I. Fleming, S. Gonsior, B.-H. Kim, A.-Y. Sung, H.-G. Woo, *Org. Biomol. Chem.* **2005**, *3*, 1557–1567.
- [17] B. T. Smith, J. A. Wendt, J. Aubé, *Org. Lett.* **2002**, *4*, 2577–2579.
- [18] J.-P. R. Hermet, M. J. McGrath, P. O'Brien, D. W. Porter, J. Gilday, *Chem. Commun.* **2004**, 1830–1831.
- [19] (a) C. Morley, D. W. Knight, A. C. Share, *Tetrahedron: Asymmetry* **1990**, *1*, 147–150; (b) C. Morley, D. W. Knight, A. C. Share, *J. Chem. Soc. Perkin Trans. 1* **1994**, 2903–2907.
- [20] C. Pousset, R. Callens, M. Haddad, M. Larchevêque, *Tetrahedron: Asymmetry* **2004**, *15*, 3407–3412.
- [21] CCDC 1566271 (**3**), 1566272 (**8**) and 1566273 (**13**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.
- [22] D. Gray, T. Gallagher, *Angew. Chem. Int. Ed.* **2006**, *45*, 2419–2423; *Angew. Chem.* **2006**, *118*, 2479–2483.
- [23] A step is defined as a process conducted in a single reaction vessel.
- [24] J. F. Couch, *J. Am. Chem. Soc.* **1937**, *59*, 1469–1471.
- [25] Reduction of **13** gave a 97:3 mixture of (–)-sparteine and (+)-β-isosparteine, from which (–)-sparteine bis-sulfate was isolated after acidification and recrystallisation.

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Layout 2:

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James D Firth, Steven J. Canipa, Leigh Ferris, Peter O'Brien*

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Gram-Scale Synthesis of the (-)-Sparteine Surrogate and (-)-Sparteine

Supply and demand: The first gram-scale synthesis of the (-)-sparteine surrogate and (-)-sparteine has been achieved. A convergent approach to the two diamines is reported with (-)-sparteine being obtained through a resolution/recombination strategy. This work addresses long-term supply issues relating to these widely used chiral ligands.