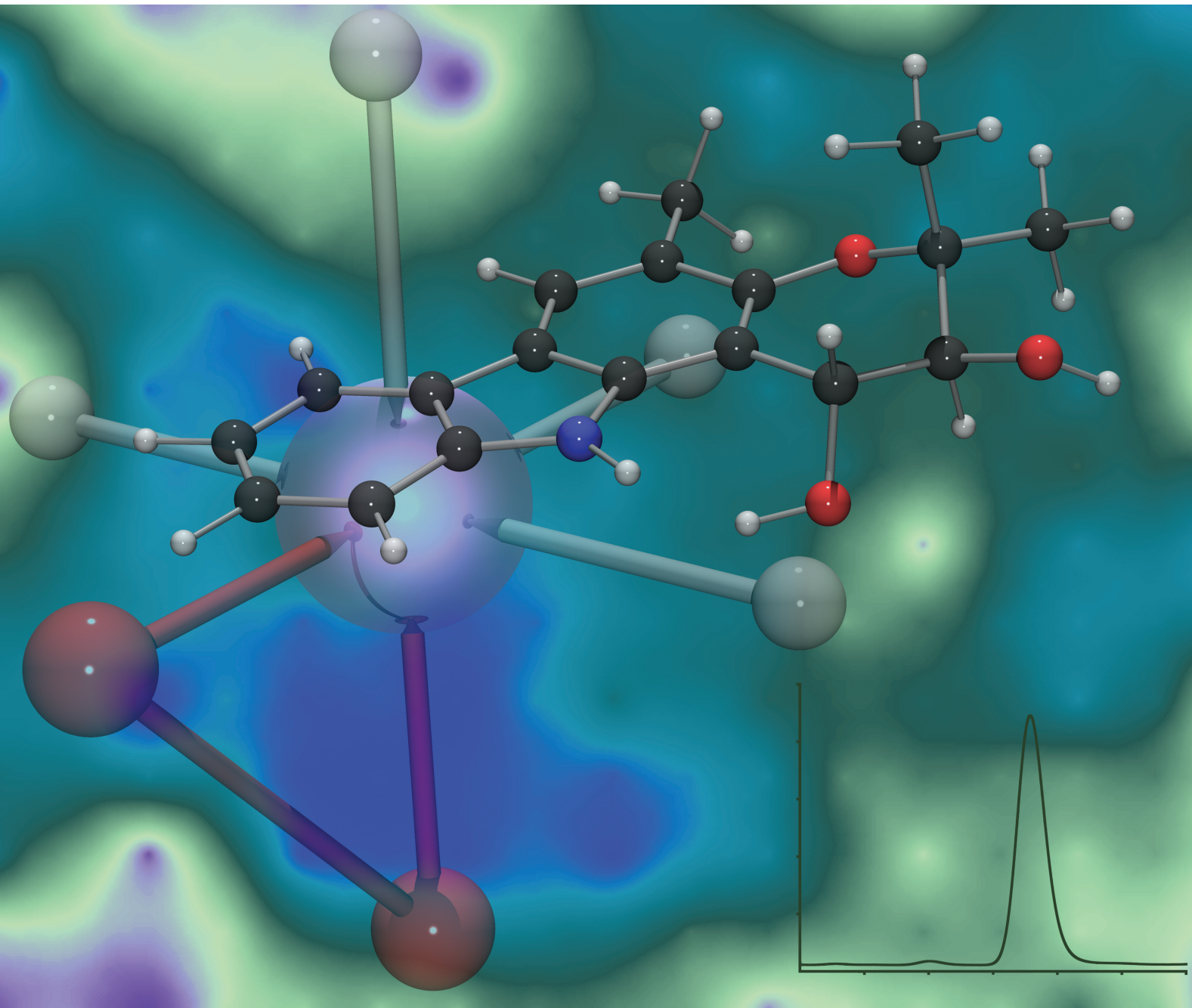


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Efficient iron-mediated approach to  
pyrano[3,2-*a*]carbazole alkaloids



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# Efficient iron-mediated approach to pyrano[3,2-*a*]carbazole alkaloids—first total syntheses of *O*-methylnurrayamine A and 7-methoxymurrayacine, first asymmetric synthesis and assignment of the absolute configuration of (–)-*trans*-dihydroxygirininimbine†‡

Konstanze K. Gruner,<sup>a</sup> Thomas Hopfmann,<sup>a</sup> Kazuhiro Matsumoto,<sup>b</sup> Anne Jäger,<sup>a</sup> Tsutomu Katsuki<sup>b</sup> and Hans-Joachim Knölker<sup>\*a</sup>

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Iron-mediated oxidative cyclisation provides an efficient approach to pyrano[3,2-*a*]carbazole alkaloids. Thus, improved routes to girininimbine and murrayacine as well as the first total syntheses of *O*-methylnurrayamine A and 7-methoxymurrayacine are reported. Asymmetric epoxidation of girininimbine led to (–)-*trans*-dihydroxygirininimbine and the assignment of its absolute configuration.

Pyrano[3,2-*a*]carbazole alkaloids are highly interesting because of their structural features, from the biogenetic point of view and due to their useful biological activities (Fig. 1).<sup>1,2</sup> Girininimbine

(1) was the first pyrano[3,2-*a*]carbazole alkaloid isolated from natural sources, by Chakraborty *et al.* from the stem bark and by Joshi *et al.* from the leaves of *Murraya koenigii*.<sup>3,4</sup> The structural assignment of girininimbine (1) was based on spectroscopic studies and chemical transformations.<sup>3,4</sup>

Further natural sources for girininimbine (1) are the roots of *Clausena heptaphylla* as well as the root bark of *Murraya euchrestifolia*.<sup>5,6</sup> More recently, girininimbine (1) was shown to exhibit antitumor activity.<sup>7</sup> Murrayacine (2) has been isolated by Chakraborty *et al.* from two different natural sources, *Murraya koenigii*<sup>3,8</sup> and *Clausena heptaphylla*.<sup>9</sup> The isolation of *O*-methylnurrayamine A (3) from the leaves of *Murraya koenigii* has been reported by Nakatani *et al.* only in 2003.<sup>10</sup> Prior to its isolation from natural sources, this alkaloid was obtained by semisynthesis *via O*-methylation of natural murrayamine A.<sup>11</sup> 7-Methoxymurrayacine (4) was obtained by Lange *et al.* in 1990 from the roots of *Murraya siamensis*.<sup>12</sup> In 1985, Furukawa *et al.* described the isolation of (–)-*trans*-dihydroxygirininimbine ((–)-5) from the roots of *Murraya euchrestifolia*.<sup>13</sup> The structural assignment was supported by epoxidation and subsequent hydrolysis of natural girininimbine (1), which afforded (±)-5 along with (±)-*cis*-dihydroxygirininimbine ((±)-6).<sup>13</sup> However, the absolute configuration of (–)-*trans*-dihydroxygirininimbine ((–)-5), which shows an optical rotation of  $[\alpha]_D = -4.0$  (MeOH), was not determined. The isolation of *cis*-dihydroxygirininimbine (6) has not been reported yet in the literature but was achieved by Furukawa and Ito in 2006.<sup>14</sup> From 1.2 kg of dried roots of *Murraya koenigii* collected in Bangladesh, they obtained 1.2 mg of *cis*-dihydroxygirininimbine (6). Because 6 showed no optical rotation and due to the absence of Cotton effects in the CD spectrum, it was concluded that this natural product is a racemate.<sup>14</sup>

The pharmacological potential of the pyrano[3,2-*a*]carbazole alkaloids has led to a strong interest in their synthesis and induced the development of several routes to girininimbine (1) as the parent compound.<sup>2,15</sup> So far, we have reported two different approaches to girininimbine (1). The first route relied on a molybdenum-mediated construction of the carbazole framework and opened the way to the first total synthesis of racemic *trans*-dihydroxygirininimbine ((±)-5).<sup>16</sup> In our second synthesis, we have used a

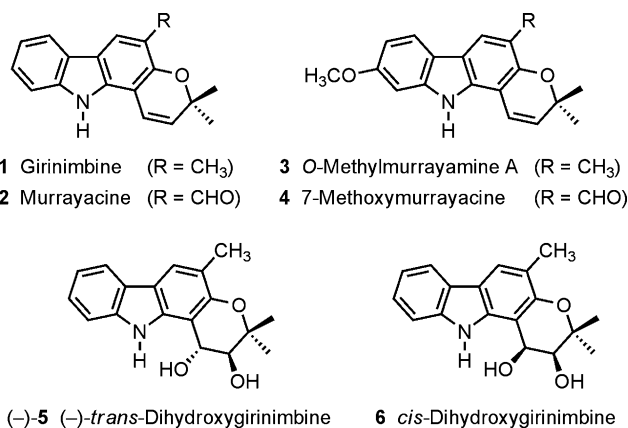


Fig. 1 Naturally occurring pyrano[3,2-*a*]carbazole alkaloids.

<sup>a</sup>Department Chemie, Technische Universität Dresden, Bergstrasse 66, 01069 Dresden, Germany. E-mail: hans-joachim.knoelker@tu-dresden.de; Fax: +49 351-463-37030

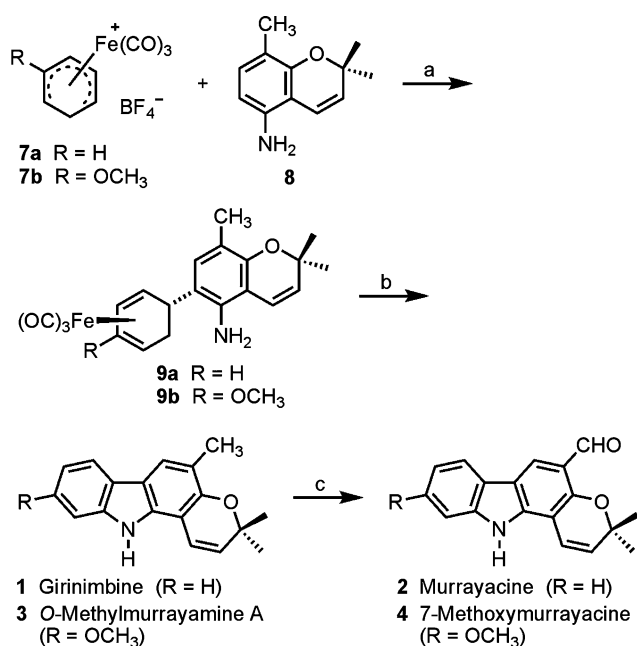
<sup>b</sup>Department of Chemistry, Faculty of Science, Graduate School and Institute for Advanced Study, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

† Part 94 of 'Transition Metals in Organic Synthesis'; for Part 93, see: ref. 1.

‡ Electronic supplementary information (ESI) available: <sup>1</sup>H and <sup>13</sup>C NMR data of compounds 1–6 and HPLC results of 6. CCDC reference number 801747. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob01088j

palladium-catalysed oxidative cyclisation as the key-step leading to euchrestifoline. This was subsequently converted to girinimbine (**1**).<sup>17</sup> In the present work, we describe an improved route to pyrano[3,2-*a*]carbazole alkaloids using our iron-mediated construction of the carbazole ring system.<sup>18</sup> Moreover, we report an asymmetric synthesis of (–)-*trans*-dihydroxygirinimbine ((–)-**5**) and the assignment of the absolute configuration for the natural product.

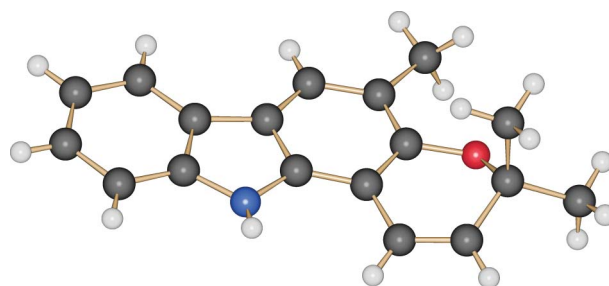
The tricarbonyliron-coordinated cyclohexadienylum salts **7a** and **7b** are readily available on a large scale *via* the 1-azabutadiene-catalysed complexation of the corresponding cyclohexadiene followed by hydride abstraction (Scheme 1).<sup>19</sup> Using the improved procedure, which has been developed in the course of our synthesis of euchrestifoline, the aminochromene **8** was prepared in three steps and 70% overall yield starting from 2-methyl-5-nitrophenol.<sup>17</sup> Reaction of the complex salts **7a** and **7b** with the aminochromene **8** in acetonitrile at room temperature afforded regioselectively the corresponding iron complexes **9a** and **9b** by electrophilic aromatic substitution. Previous work in our laboratories has shown that iron-mediated oxidative cyclisations with concomitant aromatisation leading to 2-oxygenated and 2,7-dioxygenated carbazoles are achieved best by treatment with iodine in pyridine at elevated temperature.<sup>20</sup> Thus, oxidation of the iron complexes **9a** and **9b** with iodine in pyridine at 90 °C provided girinimbine (**1**) and *O*-methylmurrayamine A (**3**) in 61% and 63% yield, respectively. Subsequent oxidation of **1** and **3** with DDQ led to murrayacine (**2**) and 7-methoxymurrayacine (**4**).



**Scheme 1** Synthesis of the pyrano[3,2-*a*]carbazoles **1–4**. *Reagents and conditions:* (a) 2.2 equiv. **8**, MeCN, rt, **a**: 1.5 h, 95% **9a**, **b**: 7.5 h, 94% **9b**; (b) 3.0 equiv. iodine, pyridine, 90 °C, 6 h, **a**: 61% **1**, **b**: 63% **3**; (c) 2.2 equiv. DDQ, MeOH–THF–H<sub>2</sub>O (3 : 1 : 1), rt, 90 min, (R = H): 96% **2**, (R = OCH<sub>3</sub>): 93% **4**.

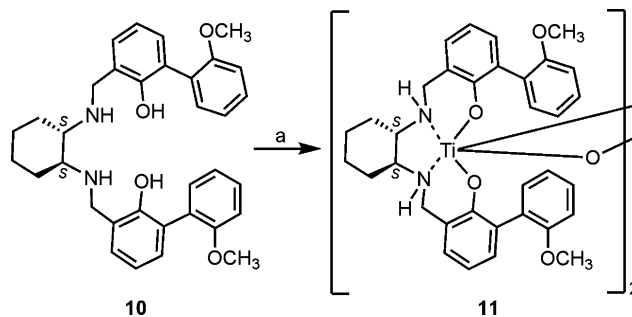
The structural assignments for the pyrano[3,2-*a*]carbazoles **1–4** were based on their spectroscopic data which are in full agreement with those reported for the corresponding natural products.<sup>§ 3–12</sup>

The structure of girinimbine (**1**) has been additionally confirmed by an X-ray crystal structure determination (Fig. 2).<sup>¶</sup>



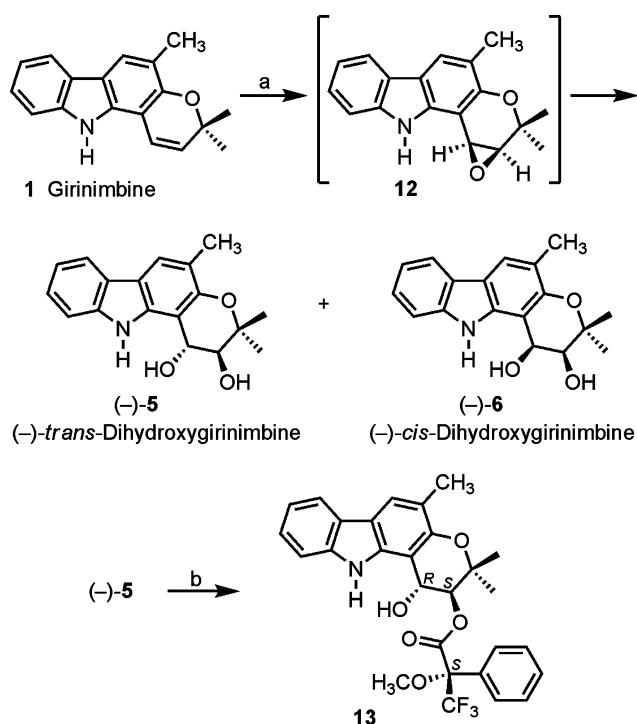
**Fig. 2** Molecular structure of girinimbine (**1**) in the crystal.

For the enantioselective synthesis of *trans*-dihydroxygirinimbine (**5**), we envisaged an asymmetric catalytic epoxidation of the corresponding chromene double bond of girinimbine (**1**). The titanium–salan catalyst **11**, which is prepared by reaction of ligand **10** with titanium tetra(isopropoxide) in the presence of water (Scheme 2), had already provided excellent results in the asymmetric catalytic epoxidation of chromenes.<sup>21</sup> Therefore, the asymmetric epoxidation of girinimbine (**1**) was carried out with hydrogen peroxide in dichloromethane at 0 °C in the presence of 5 mol% of the titanium–salan catalyst **11** with an (*S,S*)-configuration. However, after removal of the solvent, chromatography on silica gel provided no epoxide but a 1 : 1 mixture of (–)-*trans*-dihydroxygirinimbine ((–)-**5**) ( $[\alpha]_D^{20} = -2.0$ ,  $c = 1$ , MeOH) and (–)-*cis*-dihydroxygirinimbine ((–)-**6**) (both in 12% yield) along with more than 70% of recovered girinimbine (**1**) (Scheme 3). Presumably, the diastereoisomeric diol mixture is formed by opening of the initially formed epoxide **12** to an intermediate benzylic cation followed by a non-diastereoselective attack of water. Employment of a phosphate buffer (pH = 7.4), conditions which are known to avoid *in situ* hydrolysis of the epoxide,<sup>22</sup> also led to the 1 : 1 mixture of the diols (–)-**5** and (–)-**6**. All attempts to improve the turnover by modification of the reaction conditions (temperature, reaction time, amount of catalyst **11**) gave no improvement (yields were ranging from 8–13%). Although the yield was only moderate, it was obvious that epoxidation in the presence of the (*S,S*)-titanium–salan catalyst **11** provided preferentially the natural enantiomer of *trans*-dihydroxygirinimbine: (–)-**5**. Consequently, asymmetric epoxidation using the enantiomeric titanium–salan catalyst with



**Scheme 2** Preparation of the (*S,S*)-titanium–salan complex **11**. *Reagents and conditions:* (a) 1.2 equiv. (*S,S*)-salan ligand **10**, 1.0 equiv. Ti(Oi-Pr)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h, then addition of a few drops of H<sub>2</sub>O; the resulting complex **11** was used *in situ*.



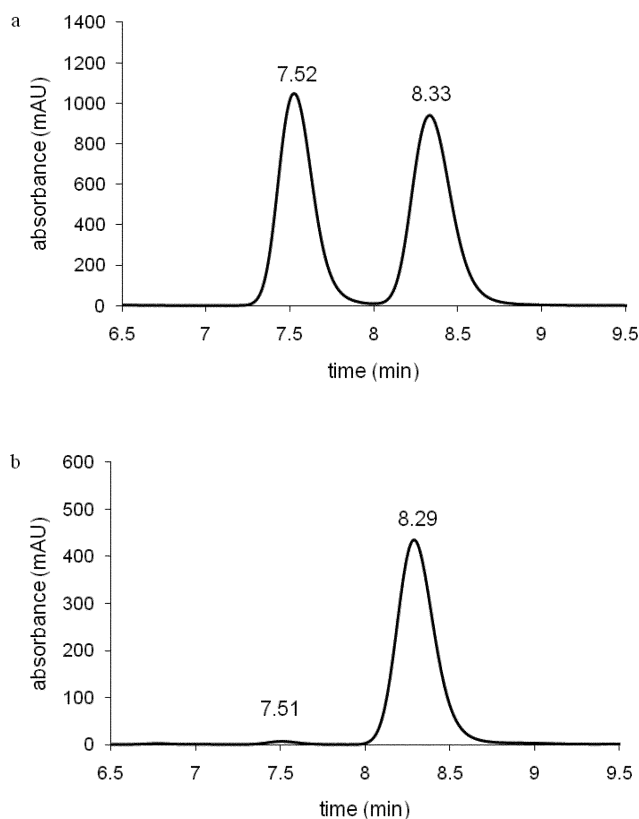


**Scheme 3** Asymmetric epoxidation of girinimbine (**1**) to (-)-**5** and (-)-**6** and transformation of (-)-**5** into the (*S*)-Mosher ester **13**. Reagents and conditions: (a) 5 mol% titanium–salan catalyst **11**, 1.1 equiv.  $\text{H}_2\text{O}_2$ ,  $\text{CH}_2\text{Cl}_2$ , 0 °C, 48 h, 12% (-)-**5** (98% ee), 12% (-)-**6** (98% ee); (b) 3.0 equiv. (*R*)-(-)-MTPACL, 3.0 equiv.  $\text{Et}_3\text{N}$ , cat. DMAP, THF, rt, 48 h, 74%.

the (*R,R*)-configuration afforded (+)-*trans*-dihydroxygirinimbine ((+)-**5**). The dihydroxygirinimbines (-)-**5** and (-)-**6** are unequivocally characterised by their spectroscopic data,<sup>||</sup> which have been compared with those of the natural products (for the spectroscopic data of natural *cis*-dihydroxygirinimbine (**6**), see ESI<sup>†</sup>).<sup>13,14</sup>

The enantiomeric excess of our synthetic (-)-*trans*-dihydroxygirinimbine ((-)-**5**) has been determined by chiral HPLC. A complete base line separation of the two enantiomers of ( $\pm$ )-*trans*-dihydroxygirinimbine (( $\pm$ )-**5**)<sup>16</sup> has been achieved using a Nucleocel reversed phase column and optimised parameters (Fig. 3). It has been shown that our synthetic (-)-**5** had an enantiomeric excess of 98%. An alternative set of experimental conditions for the chiral HPLC led to a separation of the two enantiomers of *cis*-dihydroxygirinimbine (**6**) (see ESI<sup>†</sup>). Thus, we could confirm that the diastereoisomer (-)-**6** was obtained in the same enantiomeric excess of 98%. This observation supports our hypothesis that both diastereoisomeric diols are generated by a non-diastereoselective hydrolysis of the initially formed epoxide **12**. Moreover, the optical rotation of  $[\alpha]_{\text{D}}^{20} = -12.0$  ( $c = 0.5$ , MeOH) of our synthetic (-)-**6** supports the assumption of Furukawa and Ito that the natural product has been obtained as a racemate.<sup>14</sup>

Finally, we have assigned the absolute configuration of the natural product using the method described by Mosher.<sup>23</sup> Reaction of (-)-*trans*-dihydroxygirinimbine ((-)-**5**) with (*R*)-(-)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetyl chloride ((*R*)-(-)-MTPACL) led to a regioselective monoacylation of the homobenzylic hydroxy group and afforded the corresponding (*S*)-Mosher ester **13** (Scheme 3).<sup>\*\*</sup> Comparison of the <sup>1</sup>H NMR spectrum of compound **13** with that of the diastereoisomeric mixture of (*S*)-Mosher



**Fig. 3** Chiral HPLC of *trans*-dihydroxygirinimbine (**5**) using a Nucleocel  $\delta$ -RP column from Macherey-Nagel, dimension:  $250 \times 4.6$  mm,  $T = 35$  °C, eluent: MeCN– $\text{H}_2\text{O}$  (65 : 35), rate:  $0.8 \text{ mL min}^{-1}$ ,  $\lambda = 260$  nm; (a) ( $\pm$ )-*trans*-dihydroxygirinimbine (( $\pm$ )-**5**); (b) (-)-*trans*-dihydroxygirinimbine ((-)-**5**).

esters obtained from ( $\pm$ )-*trans*-dihydroxygirinimbine (( $\pm$ )-**5**)<sup>16</sup> led us to assign an *S*-configuration to the stereogenic center at the homobenzylic position of **13** (see ESI<sup>†</sup>). The *R*-configuration of the stereogenic center at the benzylic position results from the *trans* relationship of the two hydroxy groups in (-)-**5**. Both diastereoisomeric diols, (-)-**5** and (-)-**6**, are presumably generated from the intermediate epoxide **12** by cleavage of the benzylic C–O bond and subsequent non-diastereoselective attack of water at the resulting benzylic cation. Thus, the obtained (-)-*cis*-dihydroxygirinimbine ((-)-**6**) is assumed to have an (*S,S*)-configuration.

In conclusion, we have developed a highly efficient route to pyrano[3,2-*a*]carbazole alkaloids. The iron-mediated synthesis provides girinimbine (**1**) in 2 steps and 58% overall yield based on the aminochromene **8** (previous routes: 2 steps and 11% overall yield,<sup>16</sup> 3 steps and 26% overall yield<sup>17</sup>). Moreover, we have improved the access to murrayacine (**2**) and described the first total syntheses of *O*-methylmurrayacine A (**3**) (2 steps and 59% overall yield based on **8**) and 7-methoxymurrayacine (**4**) (3 steps and 55% overall yield based on **8**). Although in only moderate yield, asymmetric epoxidation of girinimbine (**1**) affords (-)-*trans*-dihydroxygirinimbine ((-)-**5**) in 98% ee. The absolute configuration of the natural product has been assigned by the Mosher method.

We are indebted to Professor Hiroshi Furukawa and Professor Chihiro Ito (Faculty of Pharmacy, Meijo University, Nagoya, Japan) for communicating to us prior to publication details of their isolation and the spectroscopic data of natural

*cis*-dihydroxygirininimbine. We would like to thank B. Sc. Sebastian Kutz for experimental support. H.-J. K. is grateful to the Japan Society for the Promotion of Science (JSPS) for a fellowship.

## Notes and references

§ Spectroscopic data for girininimbine (1): Colourless crystals, mp 176 °C (ref. 3a: 176 °C); UV (EtOH):  $\lambda = 237, 287, 327, 342, 358, 384$  nm; IR (KBr):  $\nu = 3317, 2974, 1642, 1609, 1495, 1460, 1440, 1404, 1360, 1345, 1321, 1243, 1227, 1210, 1191, 1176, 1158, 1145, 1121, 1058, 1023, 882, 757, 742, 725, 689, \text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.48$  (s, 6 H), 2.33 (s, 3 H), 5.69 (d,  $J = 9.7$  Hz, 1 H), 6.62 (d,  $J = 9.7$  Hz, 1 H), 7.17 (t,  $J = 7.0$  Hz, 1 H), 7.30 (t,  $J = 7.0$  Hz, 1 H), 7.37 (d,  $J = 7.0$  Hz, 1 H), 7.66 (s, 1 H), 7.87 (br s, 1 H), 7.90 (d,  $J = 7.0$  Hz, 1 H);  $^{13}\text{C NMR}$  and DEPT (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 16.07$  ( $\text{CH}_3$ ), 27.58 (2  $\text{CH}_3$ ), 75.84 (C), 104.41 (C), 110.36 (CH), 116.71 (C), 117.21 (CH), 118.59 (C), 119.30 (CH), 119.46 (CH), 121.13 (CH), 123.88 (C), 124.23 (CH), 129.40 (CH), 134.78 (C), 139.42 (C), 149.77 (C); MS (EI):  $m/z$  (%) = 263 ( $\text{M}^+$ , 26), 248 (100), 85 (15); HRMS:  $m/z$  calc. for  $\text{C}_{18}\text{H}_{17}\text{NO}$  ( $\text{M}^+$ ): 263.1310; found: 263.1288.

Spectroscopic data for murrayacine (2): Colourless crystals, mp 248–250 °C (ref. 3c, 8, 9: 244–245 °C); UV (EtOH):  $\lambda = 225, 242$  (sh), 282, 302, 347 (sh), 364 nm; IR (ATR):  $\nu = 3217, 3156, 2955, 2921, 2853, 1663, 1635, 1602, 1575, 1474, 1453, 1408, 1374, 1352, 1331, 1233, 1198, 1186, 1160, 1118, 1047, 1012, 893, 854, 833, 735, 690, 655, 561 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.55$  (s, 6 H), 5.80 (d,  $J = 9.9$  Hz, 1 H), 6.62 (d,  $J = 9.9$  Hz, 1 H), 7.23–7.29 (m, 1 H), 7.36–7.40 (m, 2 H), 7.97 (d,  $J = 7.8$  Hz, 1 H), 8.15 (br s, 1 H), 8.42 (s, 1 H), 10.49 (s, 1 H);  $^{13}\text{C NMR}$  and DEPT (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 27.65$  (2  $\text{CH}_3$ ), 77.56 (C), 104.12 (C), 110.71 (CH), 116.15 (CH), 118.17 (C), 118.66 (C), 119.82 (CH), 120.26 (CH), 120.93 (CH), 124.05 (C), 125.95 (CH), 130.12 (CH), 140.03 (C), 140.20 (C), 154.79 (C), 189.24 (CHO); MS (EI):  $m/z$  (%) = 277 ( $\text{M}^+$ , 13), 262 (100), 260 (25), 204 (19); anal. calc. for  $\text{C}_{18}\text{H}_{15}\text{NO}_2$ : C 77.96, H 5.45, N 5.05, found: C 77.93, H 5.34, N 4.91.

Spectroscopic data for *O*-methylmurrayamine A (3): Colourless crystals, mp 253–255 °C (ref. 11: 232–233 °C); UV (EtOH):  $\lambda = 220, 241, 244$  (sh), 284 (sh), 293, 341, 357 (sh) nm; IR (KBr):  $\nu = 3387, 3007, 2974, 2925, 1645, 1626, 1452, 1433, 1270, 1213, 1195, 1159, 1060, 1030, 1014, 831 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz, acetone- $d_6$ ):  $\delta = 1.48$  (s, 6 H), 2.30 (s, 3 H), 3.86 (s, 3 H), 5.78 (d,  $J = 9.8$  Hz, 1 H), 6.77 (dd,  $J = 8.5$  Hz, 2.2 Hz, 1 H), 6.90 (d,  $J = 9.8$  Hz, 1 H), 6.96 (d,  $J = 2.2$  Hz, 1 H), 7.63 (s, 1 H), 7.82 (d,  $J = 8.5$  Hz, 1 H), 10.15 (br s, 1 H);  $^{13}\text{C NMR}$  and DEPT (125 MHz, acetone- $d_6$ ):  $\delta = 16.17$  ( $\text{CH}_3$ ), 27.81 (2  $\text{CH}_3$ ), 55.64 ( $\text{CH}_3$ ), 76.29 (C), 95.60 (CH), 105.46 (C), 108.23 (CH), 117.71 (C), 118.06 (C), 118.23 (C), 118.62 (CH), 120.49 (CH), 120.96 (CH), 129.90 (CH), 136.18 (C), 142.26 (C), 149.43 (C), 159.02 (C); MS (EI):  $m/z$  (%) = 293 ( $\text{M}^+$ , 32), 278 (65), 263 (31), 248 (100), 211 (14), 189 (12), 170 (18); HRMS:  $m/z$  calc. for  $\text{C}_{19}\text{H}_{19}\text{NO}_2$  ( $\text{M}^+$ ): 293.1416; found: 293.1405.

Spectroscopic data for 7-methoxymurrayacine (4): Yellow plates, mp 237–239 °C (from MeOH–THF, 8 : 1) (ref. 12: 211–213 °C); UV (EtOH):  $\lambda = 225, 235, 247$  (sh), 290 (sh), 304, 337 (sh), 354 nm; IR (KBr):  $\nu = 3188, 2924, 2856, 1659, 1633, 1601, 1578, 1426, 1202, 1157, 1052, 814 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 1.49$  (s, 6 H), 3.84 (s, 3 H), 5.93 (d,  $J = 9.9$  Hz, 1 H), 6.80 (dd,  $J = 8.5$  Hz, 2.3 Hz, 1 H), 6.93 (d,  $J = 9.9$  Hz, 1 H), 6.94 (s, 1 H), 7.99 (d,  $J = 8.5$  Hz, 1 H), 8.21 (s, 1 H), 10.35 (s, 1 H), 11.66 (s, 1 H);  $^{13}\text{C NMR}$  and DEPT (125 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 27.21$  (2  $\text{CH}_3$ ), 55.32 ( $\text{CH}_3$ ), 76.97 (C), 95.32 (CH), 104.12 (C), 108.43 (CH), 116.66 (C), 116.79 (CH), 117.39 (C), 117.83 (CH), 117.86 (C), 121.08 (CH), 130.08 (CH), 140.71 (C), 142.16 (C), 153.18 (C), 158.64 (C), 187.96 (CHO); MS (EI):  $m/z$  (%) = 307 ( $\text{M}^+$ , 60), 292 (100), 264 (7); HRMS:  $m/z$  calc. for  $\text{C}_{19}\text{H}_{17}\text{NO}_3$  ( $\text{M}^+$ ): 307.1208; found: 307.1197.

¶ Crystal data for girininimbine (1):  $\text{C}_{18}\text{H}_{17}\text{NO}$ , crystal size:  $0.42 \times 0.17 \times 0.09 \text{ mm}^3$ ,  $M = 263.33 \text{ g mol}^{-1}$ , monoclinic, space group:  $Cc$ ,  $\lambda = 0.71073 \text{ \AA}$ ,  $a = 11.960(2)$ ,  $b = 16.344(3)$ ,  $c = 7.655(2) \text{ \AA}$ ,  $\beta = 109.03(3)^\circ$ ,  $V = 1414.6(5) \text{ \AA}^3$ ,  $Z = 4$ ,  $\rho_c = 1.236 \text{ g cm}^{-3}$ ,  $\mu = 0.076 \text{ mm}^{-1}$ ,  $T = 198(2) \text{ K}$ ,  $\theta$  range =  $3.07$ – $28.00^\circ$ ; reflections collected: 24148, independent: 3367 ( $R_{\text{int}} = 0.0753$ ). The structure was solved by direct methods and refined by full-matrix least-squares on  $F^2$ ;  $R_1 = 0.0375$ ,  $wR_2 = 0.0747$  [ $I > 2\sigma(I)$ ]; maximal residual electron density:  $0.127 \text{ e \AA}^{-3}$ . CCDC 801747.

|| Spectroscopic data for (–)-*trans*-dihydroxygirininimbine (–)-5: Colourless crystals, mp 170–172 °C;  $[\alpha]_D^{20} = -2.0$  ( $c = 1$ , MeOH) (ref. 13: mp 189–190 °C;  $[\alpha]_D = -4.0$ , MeOH); UV (MeOH):  $\lambda = 216, 42, 254$  (sh), 260, 304, 333 nm; IR (ATR):  $\nu = 3488, 3369, 2977, 2918, 2851, 1630, 1609, 1576, 1460, 1436, 1390, 1372, 1345, 1308, 1211, 1179, 1140, 1114, 1070, 1020, 1003,$

$992, 952, 875, 740, 710, 596 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz, acetone- $d_6$ ):  $\delta = 1.27$  (s, 3 H), 1.55 (s, 3 H), 2.31 (s, 3 H), 3.80 (d,  $J = 8.0$  Hz, 1 H), 4.96 (d,  $J = 8.0$  Hz, 1 H), 7.13 (m, 1 H), 7.28 (m, 1 H), 7.56 (d,  $J = 8.1$  Hz, 1 H), 7.77 (s, 1 H), 7.97 (d,  $J = 7.8$  Hz, 1 H), 9.88 (br s, 1 H);  $^{13}\text{C NMR}$  and DEPT (125 MHz, acetone- $d_6$ ):  $\delta = 16.78$  ( $\text{CH}_3$ ), 19.34 ( $\text{CH}_3$ ), 27.17 ( $\text{CH}_3$ ), 69.77 (CH), 77.12 (CH), 79.41 (C), 107.21 (C), 111.61 (CH), 116.88 (C), 118.24 (C), 119.32 (CH), 119.57 (CH), 121.33 (CH), 123.94 (C), 124.51 (CH), 138.86 (C), 140.69 (C), 150.25 (C); MS (EI):  $m/z$  (%) = 297 ( $\text{M}^+$ , 67), 279 (11), 226 (18), 225 (100), 210 (11); anal. calc. for  $\text{C}_{18}\text{H}_{19}\text{NO}_3$ : C, 72.21, H 6.44, N 4.71, found: C 73.06, H 6.66, N 5.14.

Spectroscopic data for (–)-*cis*-dihydroxygirininimbine (–)-6: Colourless crystals, mp 160 °C;  $[\alpha]_D^{20} = -12.0$  ( $c = 0.5$ , MeOH); UV (MeOH):  $\lambda = 214, 233$  (sh), 239, 254 (sh), 260, 267 (sh), 304, 333 nm; IR (ATR):  $\nu = 3436, 3380, 2978, 2909, 1660, 1630, 1609, 1578, 1493, 1472, 1457, 1442, 1431, 1379, 1306, 1206, 1163, 1146, 1102, 1064, 1038, 1014, 996, 933, 920, 902, 875, 845, 795, 743, 728, 604, 581, \text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz, acetone- $d_6$ ):  $\delta = 1.37$  (s, 3 H), 1.55 (s, 3 H), 2.30 (s, 3 H), 3.87 (br d,  $J = 4.7$  Hz, 1 H), 4.19 (m, 1 H), 4.29 (m, 1 H), 5.22 (br d,  $J = 4.7$  Hz, 1 H), 7.28 (m, 1 H), 7.57 (d,  $J = 8.1$  Hz, 1 H), 7.77 (s, 1 H), 7.97 (d,  $J = 7.7$  Hz, 1 H), 9.83 (br s, 1 H);  $^{13}\text{C NMR}$  and DEPT (125 MHz, acetone- $d_6$ ):  $\delta = 16.83$  ( $\text{CH}_3$ ), 24.48 (2  $\text{CH}_3$ ), 65.21 (CH), 71.83 (CH), 78.38 (C), 105.70 (C), 111.64 (CH), 116.71 (C), 118.28 (C), 119.33 (CH), 119.53 (CH), 121.27 (CH), 124.09 (C), 124.44 (CH), 139.77 (C), 140.77 (C), 150.53 (C); MS (EI):  $m/z$  (%) = 297 ( $\text{M}^+$ , 73), 279 (20), 226 (33), 225 (100), 210 (18); HRMS:  $m/z$  calc. for  $\text{C}_{18}\text{H}_{19}\text{NO}_3$ : 297.1365; found: 297.1347.

\*\* Spectroscopic data for the (S)-Mosher ester 13: Yellow oil;  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.17$  (s, 3 H), 1.34 (s, 3 H), 2.29 (s, 3 H), 3.64 (s, 3 H), 5.10 (br d,  $J = 8.3$  Hz, 1 H), 5.36 (d,  $J = 8.8$  Hz, 1 H), 7.17 (t,  $J = 7.7$  Hz, 1 H), 7.32 (t,  $J = 8.0$  Hz, 1 H), 7.39 (d,  $J = 8.0$  Hz, 1 H), 7.45–7.47 (m, 3 H), 7.66–7.68 (m, 2 H), 7.74 (s, 1 H), 7.92 (d,  $J = 7.7$  Hz, 1 H), 8.72 (br s, 1 H);  $^{13}\text{C NMR}$  and DEPT (150 MHz,  $\text{CDCl}_3$ ):  $\delta = 16.45$  ( $\text{CH}_3$ ), 19.47 ( $\text{CH}_3$ ), 26.25 ( $\text{CH}_3$ ), 55.57 ( $\text{CH}_3$ ), 68.63 (CH), 77.33 (C), 79.84 (CH), 84.86 (q,  $^2J_{\text{CF}} = 31.6$  Hz, C), 104.24 (C), 110.57 (CH), 116.95 (C), 118.42 (C), 119.36 (CH), 119.41 (CH), 121.99 (CH), 123.05 (C), 124.48 (CH), 127.44 (2 CH), 128.57 (2 CH), 129.88 (CH), 131.99 (C), 137.20 (C), 139.43 (C), 148.83 (C), 166.99 (C=O), signal for the  $\text{CF}_3$  group not visible;  $^{19}\text{F NMR}$  (282 MHz,  $\text{CDCl}_3$ ):  $\delta = -71.01$  (s).

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