Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 9 | Number 7 | 7 April 2011 | Pages 2009-2556



ISSN 1477-0520

RSCPublishing

COMMUNICATION H.-J. Knölker *et al.* Efficient iron-mediated approach to pyrano[3,2-*a*]carbazole alkaloids





1477-0520(2011)9:7;1-B

Cite this: Org. Biomol. Chem., 2011, 9, 2057

www.rsc.org/obc

COMMUNICATION

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

Konstanze K. Gruner,^a Thomas Hopfmann,^a Kazuhiro Matsumoto,^b Anne Jäger,^a Tsutomu Katsuki^b and Hans-Joachim Knölker*a

Received 25th November 2010, Accepted 5th January 2011 DOI: 10.1039/c0ob01088j

Iron-mediated oxidative cyclisation provides an efficient approach to pyrano[3,2-a]carbazole alkaloids. Thus, improved routes to girinimbine and murrayacine as well as the first total syntheses of O-methylmurrayamine A and 7methoxymurrayacine are reported. Asymmetric epoxidation of girinimbine led to (-)-trans-dihydroxygirinimbine 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).^{1,2} Girinimbine



1 Girinimbine $(R = CH_3)$ 2 Murrayacine (R = CHO) 3 O-Methylmurrayamine A ($R = CH_3$) 4 7-Methoxymurrayacine (R = CHO)



6 cis-Dihydroxygirinimbine (-)-5 (-)-trans-Dihydroxygirinimbine

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

‡ Electronic supplementary information (ESI) available: ¹H and ¹³C 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

(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.^{3,4} The structural assignment of girinimbine (1) was based on spectroscopic studies and chemical transformations.3,4

Further natural sources for girinimbine (1) are the roots of Clausena heptaphylla as well as the root bark of Murraya euchrestifolia.^{5,6} More recently, girinimbine (1) was shown to exhibit antitumor activity.7 Murrayacine (2) has been isolated by Chakraborty et al. from two different natural sources, Murraya koenigii^{3c,8} and Clausena heptaphylla.⁹ The isolation of Omethylmurrayamine A (3) from the leaves of Murraya koenigii has been reported by Nakatani et al. only in 2003.¹⁰ Prior to its isolation from natural sources, this alkaloid was obtained by semisynthesis via O-methylation of natural murrayamine A.¹¹ 7-Methoxymurrayacine (4) was obtained by Lange et al. in 1990 from the roots of Murraya siamensis.12 In 1985, Furukawa et al. described the isolation of (-)-trans-dihydroxygirinimbine ((-)-5) from the roots of Murraya euchrestifolia.13 The structural assignment was supported by epoxidation and subsequent hydrolysis of natural girinimbine (1), which afforded (\pm) -5 along with (\pm) *cis*-dihydroxygirinimbine $((\pm)-6)$.¹³ However, the absolute configuration of (-)-trans-dihydroxygirinimbine ((-)-5), which shows an optical rotation of $[\alpha]_{\rm D} = -4.0$ (MeOH), was not determined. The isolation of *cis*-dihydroxygirinimbine (6) has not been reported yet in the literature but was achieved by Furukawa and Ito in 2006.14 From 1.2 kg of dried roots of Murrava koenigii collected in Bangladesh, they obtained 1.2 mg of cis-dihydroxygirinimbine (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.14

The pharmacological potential of the pyrano[3,2-a]carbazolealkaloids has led to a strong interest in their synthesis and induced the development of several routes to girinimbine (1) as the parent compound.^{2,15} So far, we have reported two different approaches to girinimbine (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-dihydroxygirinimbine $((\pm)-5)$.¹⁶ In our second synthesis, we have used

^aDepartment Chemie, Technische Universität Dresden, Bergstrasse 66, 01069 Dresden, Germany. E-mail: hans-joachim.knoelker@tu-dresden.de; Fax: +49 351-463-37030

^bDepartment 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.

palladium-catalysed oxidative cyclisation as the key-step leading to euchrestifoline. This was subsequently converted to girinimbine (1).¹⁷ 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.¹⁸ Moreover, we report an asymmetric synthesis of (–)-*trans*-dihydroxygirinimbine ((–)-**5**) and the assignment of the absolute configuration for the natural product.

The tricarbonvliron-coordinated cvclohexadienvlium salts 7a and 7b are readily available on a large scale via the 1-azabutadienecatalysed complexation of the corresponding cyclohexadiene followed by hydride abstraction (Scheme 1).¹⁹ 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-5nitrophenol.¹⁷ 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 2,7dioxygenated carbazoles are achieved best by treatment with iodine in pyridine at elevated temperature.²⁰ 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–H₂O (3:1:1), rt, 90 min, (R = H): 96% 2, (R = OCH₃): 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.§ $^{3-12}$

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



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.²¹ 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,²² 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)-titaniumsalan 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. $Ti(Oi-Pr)_4$, CH₂Cl₂, rt, 1 h, then addition of a few drops of H₂O; 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. H_2O_2 , CH_2Cl_2 , 0 °C, 48 h, 12% (-)-5 (98% ee), 12% (-)-6 (98% ee); (b) 3.0 equiv. (*R*)-(-)-MTPACl, 3.0 equiv. Et₃N, 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, \parallel which have been compared with those of the natural products (for the spectroscopic data of natural *cis*-dihydroxygirinimbine (6), see ESI[‡]).^{13,14}

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)¹⁶ 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[‡]). Thus, we could confirm that the diastereoisomer (-)-6 was obtained in the same enantiomeric excess of 98% ee. 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 $[\alpha]_{D}^{20} = -12.0$ (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.14

Finally, we have assigned the absolute configuration of the natural product using the method described by Mosher.²³ Reaction of (-)-*trans*-dihydroxygirinimbine ((-)-**5**) with (R)-(-)- α -methoxy- α -(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).** Comparison of the ¹H 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 δ -RP column from Macherey-Nagel, dimension: 250 × 4.6 mm, T = 35 °C, eluent: MeCN–H₂O (65:35), rate: 0.8 mL min⁻¹, $\lambda = 260$ nm; (a) (±)-*trans*-dihydroxygirinimbine ((±)-**5**); (b) (–)-*trans*-dihydroxygirinimbine ((–)-**5**).

esters obtained from (±)-*trans*-dihydroxygirinimbine ((±)-**5**)¹⁶ led us to assign an *S*-configuration to the stereogenic center at the homobenzylic position of **13** (see ESI[‡]). 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,¹⁶ 3 steps and 26% overall yield¹⁷). Moreover, we have improved the access to murrayacine (2) and described the first total syntheses of *O*-methylmurrayamine 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*-dihydroxygirinimbine. 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 girinimbine (1): Colourless crystals, mp 176 °C (ref. 3*a*: 176 °C); UV (EtOH): $\lambda = 237$, 287, 327, 342, 358, 384 nm; IR (KBr): *v* = 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, cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 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); ¹³C NMR and DEPT $(125 \text{ MHz}, \text{CDCl}_3): \delta = 16.07 (\text{CH}_3), 27.58 (2 \text{ CH}_3), 75.84 (\text{C}), 104.41 (\text{C}), 104.41 (\text{C}))$ 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 (M⁺, 26), 248 (100), 85 (15); HRMS: m/z calc. for C₁₈H₁₇NO (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): *v* = 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 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 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); ¹³C NMR and DEPT (125 MHz, CDCl₃): δ = 27.65 (2 CH₃), 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 (M⁺, 13), 262 (100), 260 (25), 204 (19); anal. calc. for C₁₈H₁₅NO₂: 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): λ = 220, 241, 244 (sh), 284 (sh), 293, 341, 357 (sh) nm; IR (KBr): ν = 3387, 3007, 2974, 2925, 1645, 1626, 1452, 1433, 1270, 1213, 1195, 1159, 1060, 1030, 1014, 831 cm⁻¹; ¹H NMR (500 MHz, acetone-d₀): δ = 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); ¹³C NMR and DEPT (125 MHz, acetone-d₆): δ = 16.17 (CH₃), 27.81 (2 CH₃), 55.64 (CH₃), 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 (M⁺, 32), 278 (65), 263 (31), 248 (100), 211 (14), 189 (12), 170 (18); HRMS: *m/z* calc. for C₁₉H₁₉NO₂ (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): λ = 225, 235, 247 (sh), 290 (sh), 304, 337 (sh), 354 nm; IR (KBr): v = 3188, 2924, 2856, 1659, 1633, 1601, 1578, 1426, 1202, 1157, 1052, 814 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ = 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), 6.90 (d, J = 8.5 Hz, 2.3 Hz, 1 H), 6.93 (d, J = 9.9 Hz, 1 H), 5.32 (CH₃), 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 (M⁺, 60), 292 (100), 264 (7); HRMS: m/z calc. for C₁₉H₁₇NO₃ (M⁺): 307.1208; found: 307.1197.

¶ Crystal data for girinimbine (1): $C_{18}H_{17}NO$, crystal size: $0.42 \times 0.17 \times 0.09 \text{ mm}^3$, $M = 263.33 \text{ g mol}^{-1}$, monoclinic, space group: Cc, $\lambda = 0.71073 \text{ Å}$, a = 11.960(2), b = 16.344(3), c = 7.655(2) Å, $\beta = 109.03(3)^\circ$, $V = 1414.6(5) \text{ Å}^3$, Z = 4, $p_c = 1.236 \text{ g cm}^{-3}$, $\mu = 0.076 \text{ mm}^{-1}$, T = 198(2) K, θ range = $3.07-28.00^\circ$; reflections collected: 24148, independent: 3367 ($R_{int} = 0.0753$). The structure was solved by direct methods and refined by full-matrix least-squares on F^2 ; $R_1 = 0.0375$, w $R_2 = 0.0747$ [$I > 2\sigma(I)$]; maximal residual electron density: 0.127e Å^{-3}. CCDC 801747.

|| Spectroscopic data for (-)-*trans*-dihydroxygirinimbine ((-)-**5**): Colourless crystals, mp 170–172 °C; $[\alpha]_D^2 = -2.0 (c = 1, \text{MeOH})$ (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 cm⁻¹; ¹H NMR (500 MHz, acetone-d₆): δ = 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 Hz)H), 7.77 (s, 1 H), 7.97 (d, J = 7.8 Hz, 1 H), 9.88 (br s, 1 H); ¹³C NMR and DEPT (125 MHz, acetone- d_6): $\delta = 16.78$ (CH₃), 19.34 (CH₃), 27.17 (CH₃), 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 (M⁺, 67), 279 (11), 226 (18), 225 (100), 210 (11); anal. calc. for C₁₈H₁₉NO₃: C, 72.21, H 6.44, N 4.71, found: C 73.06, H 6.66, N 5.14. Spectroscopic data for (-)-cis-dihydroxygirinimbine ((-)-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): v = 3436, 3380, 2978, 2909, 1660, 1630, 1609, 1578, 1491, 1472, 1457, 1442, 1431, 1379, 1306, 1206, 1163, 1146, 1102, 1064, 1038, 1014, 996, 933, 920, 902, 875, 845, 795, 743, 728, 604, 581, cm⁻¹; ¹H 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), 7.13 (m, 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); ¹³C NMR and DEPT (125 MHz, acetone d_6): $\delta = 16.83$ (CH₃), 24.48 (2 CH₃), 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 (M⁺, 73), 279 (20), 226 (33), 225 (100), 210 (18); HRMS: m/z calc. for C₁₈H₁₉NO₃: 297.1365; found: 297.1347 * Spectroscopic data for the (S)-Mosher ester 13: Yellow oil; ¹H NMR (600 MHz, CDCl₃): δ = 1.17 (s, 3 H), 1.34 (s, 3 H), 2.29 (s, 3 H), 3.64 (s, 3 H) H), 5.10 (br d, J = 8.3 Hz, 1 H), 5.36 (d, J = 8.8 Hz, 1 H), 7.17 (t, J = 7.7Hz, 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); ¹³C NMR and DEPT (150 MHz, CDCl₃): δ = 16.45 (CH₃), 19.47 (CH₃), 26.25 (CH₃), 55.57 (CH₃), 68.63 (CH), 77.33 (C), 79.84 (CH), 84.86 $(q, {}^{2}J_{C,F} = 31.6 \text{ Hz}, \text{ C}), 104.24 \text{ (C)}, 110.57 \text{ (CH)}, 116.95 \text{ (C)}, 118.42 \text{ (C)},$ 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 CF₃ group not visible; ¹⁹F NMR

- 1 R. Forke, K. K. Gruner, K. E. Knott, S. Auschill, S. Agarwal, R. Martin, M. Böhl, S. Richter, G. Tsiavaliaris, R. Fedorov, D. J. Manstein, H. O. Gutzeit and H.-J. Knölker, *Pure Appl. Chem.*, 2010, 82, 1975.
- 2 For recent reviews, see: (a) H.-J. Knölker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303; (b) H.-J. Knölker, *Top. Curr. Chem.*, 2005, **244**, 115; (c) H.-J. Knölker and K. R. Reddy, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, Amsterdam, 2008, vol. 65, pp. 1–430.
- 3 (a) D. P. Chakraborty, B. K. Barman and P. K. Bose, *Sci. Cult. (India)*, 1964, **30**, 445; (b) N. L. Dutta and C. Quasim, *Indian J. Chem.*, 1969, **7**, 307; (c) D. P. Chakraborty, K. C. Das and B. K. Chowdhury, *J. Org. Chem.*, 1971, **36**, 725.
- 4 B. S. Joshi, V. N. Kamat and D. H. Gawad, Tetrahedron, 1970, 26, 1475.
- 5 B. S. Joshi, V. N. Kamat, D. H. Gawad and T. R. Govindachari, *Phytochemistry*, 1972, **11**, 2065.
- 6 H. Furukawa, T.-S. Wu, T. Ohta and C.-S. Kuoh, *Chem. Pharm. Bull.*, 1985, **33**, 4132.
- 7 C.-B. Cui, S.-Y. Yan, B. Cai and X.-S. Yao, J. Asian Nat. Prod. Res., 2002, 4, 233.
- 8 D. P. Chakraborty and K. C. Das, J. Chem. Soc., Chem. Commun., 1968, 967.
- 9 S. Ray and D. P. Chakraborty, Phytochemistry, 1976, 15, 356.
- 10 T. Tachibana, H. Kikuzaki, N. H. Lajis and N. Nakatani, J. Agric. Food Chem., 2003, **51**, 6461.
- 11 T.-S. Wu, Phytochemistry, 1991, 30, 1048.

(282 MHz, CDCl₃): $\delta = -71.01$ (s).

- 12 N. Ruangrungsi, J. Ariyaprayoon, G. L. Lange and M. G. Organ, J. Nat. Prod., 1990, 53, 946.
- 13 H. Furukawa, T.-S. Wu and C.-S. Kuoh, Heterocycles, 1985, 23, 1391.
- 14 H. Furukawa and C. Ito, unpublished results.
- 15 (a) N. S. Narasimhan, M. V. Paradkar and A. M. Gokhale, *Tetrahedron Lett.*, 1970, **11**, 1665; (b) D. P. Chakraborty and A. Islam, *J. Indian Chem. Soc.*, 1971, **48**, 91; (c) P. Bhattacharyya, A. Chakraborty and B. K. Choowdhury, *Indian J. Chem.*, 1984, **23B**, 849; (d) D. P. Chakraborty, S. Roy and A. K. Dutta, *J. Indian Chem. Soc.*, 1987, **64**, 215.
- 16 H.-J. Knölker and C. Hofmann, Tetrahedron Lett., 1996, 37, 7947.
- 17 K. K. Gruner and H.-J. Knölker, Org. Biomol. Chem., 2008, 6, 3902.

- 18 For reviews, see: (a) H.-J. Knölker, Chem. Soc. Rev., 1999, 28, 151; (b) H.-J. Knölker, Chem. Lett., 2009, 38, 8; for recent applications, see: (c) R. Czerwonka, K. R. Reddy, E. Baum and H.-J. Knölker, Chem. Commun., 2006, 711 (d) K. E. Knott, S. Auschill, A. Jäger and H.-J. Knölker, Chem. Commun., 2009, 1467.
- (a) H.-J. Knölker, E. Baum, P. Gonser, G. Rohde and H. Röttele, *Organometallics*, 1998, **17**, 3916; (b) H.-J. Knölker, B. Ahrens, P. Gonser, M. Heininger and P. G. Jones, *Tetrahedron*, 2000, **56**, 2259; (c) H.-J. Knölker, *Chem. Rev.*, 2000, **100**, 2941; (d) E. O. Fischer and R. D. Fischer, *Angew. Chem.*, 1960, **72**, 919.
- 20 (a) H.-J. Knölker and W. Fröhner, Synthesis, 2000, 2131; (b) H.-J. Knölker and M. P. Krahl, Synlett, 2004, 528; (c) O. Kataeva, M. P. Krahl and H.-J. Knölker, Org. Biomol. Chem., 2005, 3, 3099.
- 21 (a) K. Matsumoto, Y. Sawada and T. Katsuki, Synlett, 2006, 3545; (b) Y. Sawada, K. Matsumoto, S. Kondo, H. Watanabe, T. Ozawa, K. Suzuki, B. Saito and T. Katsuki, Angew. Chem., Int. Ed., 2006, 45, 3478; (c) K. Matsumoto, Y. Sawada and T. Katsuki, Pure Appl. Chem., 2008, 80, 1071.
- 22 Y. Shimada, S. Kondo, Y. Ohara, K. Matsumoto and T. Katsuki, *Synlett*, 2007, 2445.
- 23 J. A. Dale and H. S. Mosher, J. Am. Chem. Soc., 1973, 95, 512.