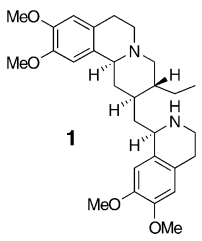
Combinatorial Synthesis

Catalyst-Controlled Stereoselective Combinatorial Synthesis**

Lutz F. Tietze, Nils Rackelmann, and Govindasamy Sekar*

Dedicated to Professor Ernst Schaumann on the occasion of his 60th birthday

Combinatorial chemistry[1] is an important method for the development of pharmaceuticals,[2] agrochemicals,[3] catalysts,[4] and materials.[5] It can be performed either on a solid phase or in solution and in some cases, the advantages of solid- and liquid-phase synthesis may be combined, if the products can be precipitated as salts.[6] The aim of combinatorial chemistry is the preparation of a multitude of organic compounds with constitutional diversity. Stereochemical aspects have so far played only a minor role, although the configuration of a molecule can have a considerable effect on its biological activity; this applies to both the absolute as well as the relative configuration.[7] Herein we present a method to access stereochemical diversity of nonpeptidic active compounds as a new combinatorial strategy.[8] By using enantiomerically pure catalysts, several stereogenic centers are constructed in a catalyst-controlled manner.[9] This general concept is introduced with the example of the synthesis of 12 stereoisomers of the biologically highly active ipecacuanha alkaloid emetine (**1**), which contains four stereogenic centers. The ruthenium complexes (*R*,*R*)-**5** and (*S*,*S*)-**5** developed by Noyori and co-workers[10] were used as catalysts. The key step of the synthesis is the enantio- or diastereoselective hydrogenation of imines, which can be prepared either by oxidation of a secondary amine or by a Bischler–Napieralski reaction.



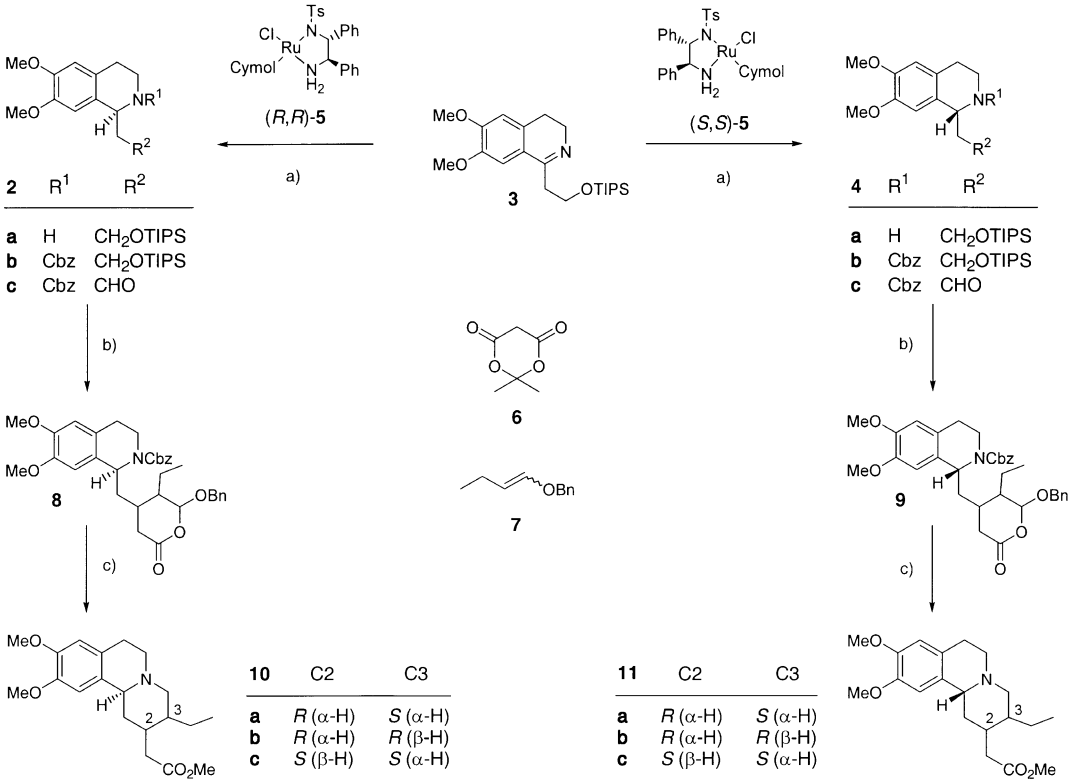
1

Oxidation of the racemic mixture of **2a** and **4a** with potassium permanganate led to the imine **3** in very good yields,[11] which was hydrogenated to the almost enantiomerically pure tetrahydroisoquinolines **2a** and **4a** by transfer hydrogenation with formic acid in the presence of the catalysts (*R*,*R*)-**5** and (*S*,*S*)-**5**, respectively (Scheme 1).[12] Protection of the secondary amino group in **2a** and **4a** with benzyloxycarbonyl chloride, cleavage of the silyl group, and subsequent oxidation of the primary alcohol yielded the

[*] Prof. Dr. L. F. Tietze, Dipl.-Chem. N. Rackelmann, Dr. G. Sekar
Institut für Organische Chemie
Georg-August-Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)
Fax: (+49) 551-399-476
E-mail: ltietze@gwdg.de

[**] The investigations were supported by the Deutsche Forschungsgemeinschaft (SFB 416) and the Fonds der Chemischen Industrie. We thank BASF, Bayer, Degussa, Symrise, and Wacker Chemie for providing us with chemicals.

  DOI: 10.1002/anie.200351129



Scheme 1. Synthesis of benzoquinolidizines **10a–c** and **11a–c**: a) **3** (1 equiv), (*R*,*R*)-**5** or (*S*,*S*)-**5**, respectively, (2.5 mol%), HCO_2H/NEt_3, DMF, room temperature, 60 min, 93%, >95% *ee*; b) **2c** or **4c** (1.1 equiv), **6** (1 equiv), **7** (10 equiv), EDDA (1 mol%), benzene, 60°C, ultrasound, 17 h, 86%; c) K_2CO_3 (0.5 equiv), MeOH; then Pd/C, H_2, 77%. DMF = *N*,*N*-dimethylformamide, EDDA = ethylenediammonium diacetate, Bn = benzyl, Cbz = benzyloxycarbonyl, TIPS = triisopropylsilyl, Ts = *p*-toluenesulfonyl, cymene = 4-isopropyltoluene.

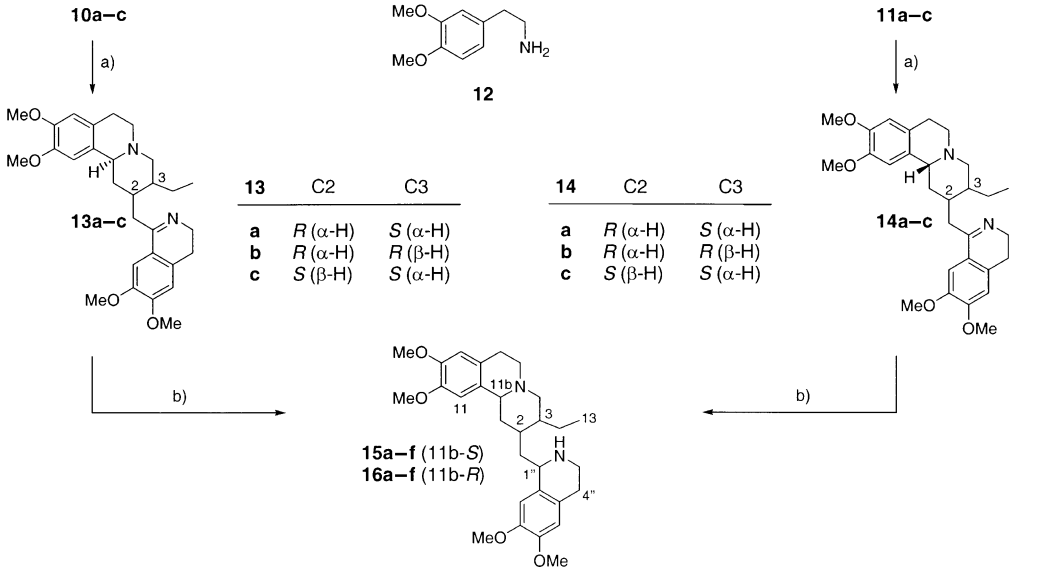
aldehydes **2c** and **4c,** respectively. A domino reaction[13] of **2c** with Meldrum acid (**6**) and the enol ether **7** in the presence of catalytic amounts of ethylenediammonium diacetate (EDDA) led to the formation of the lactone **8**, which was treated directly with methanol/potassium carbonate and then hydrogenated with Pd/C as catalyst. In this sequence, cleavage of the lactone **8** occurs first with the formation of a methyl ester and an aldehyde, which after hydrogenolysis of the Cbz protecting group reacts with the formed secondary amino function to give an enamine. This enamine is hydrogenated under the reaction conditions to form the benzoquinolizidine framework of emetine (**1**). The mixture of the three diastereomers **10a–c** (1.5:1.0:1.8) can be separated chromatographically.[14] The conversion of the enantiomeric aldehyde **4c** under identical conditions afforded the diastereomers **11a–c**.

The condensation of the diastereomeric benzoquinolizidines **10a–c** with 2-(3,4-dimethoxyphenyl)ethylamine (**12**) gave the corresponding amides, which were converted into the imines **13a–c** in a Bischler–Napieralski reaction in 60–78% yield (Scheme 2). In a similar manner, the imines **14a–c** were prepared from **11a–c**. Hydrogenation of **13a–c** with (*S*,*S*)-**5** led to **15a–c**, whereas the diastereomers **15d–f** were obtained in the presence of (*R*,*R*)-**5**.[15] Analogously, the stereoisomers **16a–c** and the corresponding diastereomers **16d–f** were obtained from **14a–c** with (*S*,*S*)-**5** and (*R*,*R*)-**5**, respectively. The yields in all hydrogenations were greater than 71%, the diastereoselectivities were, however, slightly different because of the presence of *matched* and *mismatched* combinations: Thus, in the transfer hydrogenation of **13a** with (*S*,*S*)-**5**, selectivities >98:2 were found (that is, the other possible diastereomer could not be detected), whereas in the worst case, in the reaction of **13a** with (*R*,*R*)-**5**, a ratio of 91:9 was observed.

The concept of stereoselective combinatorial synthesis, which is introduced by means of the synthesis of 12 stereoisomers of emetine (**1**), makes a large number of stereoisomers of a chiral compound accessible in a targeted manner. The reactions introduced may be varied in many ways. Thus we have also used 2-phenylethylamine, 2-(2-methoxyphenyl)-ethylamine, 2-(2,5-dimethoxyphenyl)ethylamine, and a serotonin derivative as amino components instead of **12**. The described strategy is generally applicable, and good results can be expected if the enantiomeric catalysts or reagents allow high stereochemical control, independent of the substrate.

Received: February 7, 2003 [Z51129]

Keywords: asymmetric catalysis · combinatorial chemistry · domino reactions · hydrogenation · imines



13	C2	C3
a	*R* (α-H)	*S* (α-H)
b	*R* (α-H)	*R* (β-H)
c	*S* (β-H)	*S* (α-H)

14	C2	C3
a	*R* (α-H)	*S* (α-H)
b	*R* (α-H)	*R* (β-H)
c	*S* (β-H)	*S* (α-H)

15	C2	C3	C1"	Catalyst
a	*R* (α-H)	*S* (α-H)	*R*	(*S*,*S*)-**5**
b	*R* (α-H)	*R* (β-H)	*R*	(*S*,*S*)-**5**
c	*S* (β-H)	*S* (α-H)	*R*	(*S*,*S*)-**5**
d	*R* (α-H)	*S* (α-H)	*S*	(*R*,*R*)-**5**
e	*R* (α-H)	*R* (β-H)	*S*	(*R*,*R*)-**5**
f	*S* (β-H)	*S* (α-H)	*S*	(*R*,*R*)-**5**

16	C2	C3	C1"	Catalyst
a	*R* (α-H)	*S* (α-H)	*R*	(*S*,*S*)-**5**
b	*R* (α-H)	*R* (β-H)	*R*	(*S*,*S*)-**5**
c	*S* (β-H)	*S* (α-H)	*R*	(*S*,*S*)-**5**
d	*R* (α-H)	*S* (α-H)	*S*	(*R*,*R*)-**5**
e	*R* (α-H)	*R* (β-H)	*S*	(*R*,*R*)-**5**
f	*S* (β-H)	*S* (α-H)	*S*	(*R*,*R*)-**5**

Scheme 2. Stereoselective synthesis of 12 stereoisomers of **1** (**15a–f** and **16a–f**): a) **10a–c** or **11a–c**, **12**, $AlMe_3$, reflux, 4.5 h, 60–78%; then $POCl_3$, benzene, reflux, 45 min, 60–82%; b) (*R*,*R*)-**5** or (*S*,*S*)-**5** (10 mol%), HCO_2H/NEt_3, DMF, room temperature, 60 min, 71–82%, d.r. 91:9 to >98:2.

[1] a) A. Kirschning, H. Monenschein, R. Wittenberg, *Angew. Chem.* **2001**, *113*, 670–701; *Angew. Chem. Int. Ed.* **2001**, *40*, 650–679; b) S. Senkan, *Angew. Chem.* **2001**, *113*, 322–344; *Angew. Chem. Int. Ed.* **2001**, *40*, 312–329; c) F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436–2487; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288–2337.

[2] a) J. Rademann, G. Jung, *Science* **2000**, *287*, 1947–1948; b) K. C. Nicolaou, R. Hughes, S. Y. Cho, N. Winssinger, C. Smethurst, H. Labischinski, R. Endermann, *Angew. Chem.* **2000**, *112*, 3473–3478; *Angew. Chem. Int. Ed.* **2000**, *39*, 3823–3828; c) P. N. Kaul, *Prog. Drug Res.* **1998**, *50*, 9–105.

[3] W. A. Kleschick, L. N. Davis, M. R. Dick, J. R. Garlich, E. J. Martin, N. Orr, S. C. Ng, D. J. Pernich, S. H. Unger, G. B. Watson, R. N. Zuckermann, *ACS Symp. Ser.* **2001**, *774*, 205–213.

[4] a) M. T. Reetz, *Angew. Chem.* **2001**, *113*, 292–320; *Angew. Chem. Int. Ed.* **2001**, *40*, 284–310; b) B. Jandeleit, D. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg, *Angew. Chem.* **1999**, *63*, 2494–2532; *Angew. Chem. Int. Ed.* **1999**, *111*, 2648–2689; c) P. P. Pescarna, J. C. van der Waal, I. E. Maxwell, T. Maschmeyer, *Catal. Lett.* **1999**, *63*, 1–11.

[5] a) W. F. Maier, *Angew. Chem.* **1999**, *111*, 1294–1296; *Angew. Chem. Int. Ed.* **1999**, *38*, 1216–1218; b) E. W. McFarland, W. H. Weinberg, *Trends Biotechnol.* **1999**, *17*, 107–115.

[6] L. F. Tietze, H. Evers, E. Töpken, *Angew. Chem.* **2001**, *113*, 903–905; *Angew. Chem. Int. Ed.* **2001**, *40*, 927–929.

[7] a) G. Ekatodromis, A. Borgeat, *Curr. Top. Med. Chem.* **2001**, *1*, 205–206; b) B. Testa, M. Reist, P.-A. Carrupt, *Ann. Pharm. Fr.* **2000**, *58*, 239–246; c) S. Schiffman, K. Sennewald, J. Gagnon, *Physiology and Behavior* **1981**, *27*, 51–59; d) G. Blaschke, H. P. Kraft, K. Fickentscher, F. Koehler, *Arzneim.-Forsch.* **1979**, *29*, 1640–1642.

[8] For a further approach to stereochemical combinatorial synthesis, see: U. Müllenmeister, W.-D. Fessner in *Innovation and Perspectives in Solid Phase Synthesis and Combinatorial Libraries* (Ed.: R. Epten), Mayflower Worldwide Ltd, Birmingham (UK), **2001**, p. 149–152.

[9] Reagent-controlled reactions in which enantiomerically pure auxiliaries are used are likewise possible.

[10] N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917.

[11] A solution of a racemic mixture of **2a** and **4a** (27.6 g, 70.2 mmol) in CH_3CN (650 mL) was treated at −7 °C with $KMnO_4$ (23.3 g, 147 mmol) in small portions over a period of 15 min and then stirred for 70 min at −5 °C. The reaction mixture was diluted with ice-cold Et_2O (2.5 L), the organic phase was washed with saturated NaCl solution until the solution was colorless, and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield the dihydroisoquinoline **3** as a pale yellow oil, which was used without further purification (24.7 g, 90%).

[12] A solution of dimeric dichloro(*p*-cymene)ruthenium(II) (403 mg, 0.66 mmol), 1,2-(*R*,*R*)-*N*-tosyl-1,2-diphenylethylenediamine (530 mg, 1.45 mmol), and NEt_3 (0.37 mL, 2.63 mmol) in DMF (6.1 mL) was stirred under argon for 60 min at 80 °C. The warm solution was added to the dihydroisoquinoline **3** (21.5 g, 55 mmol) in DMF (103 mL) and the mixture was cooled to 0 °C. A mixture of HCO_2H and NEt_3 (5:2; 27.5 mL) was then added dropwise, and the reaction mixture was stirred for 2 h at 25 °C. The reaction was worked up by the addition of a saturated solution of K_2CO_3, the mixture was diluted with H_2O, the aqueous phase extracted with ethyl acetate, and the combined organic phases dried over Na_2SO_4. After removal of the solvent under reduced pressure, the brown crude product was purified by chromatography on silica gel ($AcOEt/NEt_3$, 100:1) to yield **2a** as a yellow oil (20.2 g, 93%, >95% *ee*).

[13] a) L. F. Tietze, A. Modi, *Med. Res. Rev.* **2000**, *20*, 304–322; b) L. F. Tietze, F. Haunert in *Stimulating Concepts in Chemistry* (Eds. F. Vögtle, J. F. Stoddart, M. Shibasaki, Wiley-VCH, Weinheim,

2000, p. 39 – 64; c) L. F. Tietze, M. Lieb, *Curr. Opin. Chem. Biol.* **1998**, *2*, 363 – 371; d) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115 – 136; e) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137 – 170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131 – 163.

[14] **10a**: ^{1}H NMR (300 MHz, C_6D_6, TMS): $\delta = 0.82$ (t, ^3J(H,H) = 7.5 Hz, 3H; 13-H), 1.10 (m, 1H; 12-H), 1.26 (ddd, ^2J(H,H) = 13.0 Hz, ^3J(H,H) = 11.5, 11.5 Hz, 1H; 1-H_{ax}), 1.34 (m, 1H; 3-H), 1.63 (m, 1H; 12-H), 1.94 (ddd, ^2J(H,H) = 13.0 Hz, ^3J(H,H) = 3.0, 3.0 Hz, 1H; 1-H_{eq}), 2.00–2.32 (m, 6H; CH_2CO$_2$Me, 2-H; 4-H_{ax}, 6-H, 7-H), 2.55 (ddd, ^2J(H,H) = 11.5 Hz, ^3J(H,H) = 5.5, 5.5 Hz, 1H; 6-H), 2.77 (dd, ^2J(H,H) = 11.5 Hz, ^3J(H,H) = 3.5 Hz, 1H; 4-H_{eq}), 2.90–3.10 (m, 2H, 7-H; 11b-H), 3.27 (s, 3H; OMe), 3.38 (s, 3H; OMe), 6.31 (s, 1H; 8-H), 6.62 ppm (s, 1H; 11-H); ^{13}C NMR (75 MHz, C_6D_6, TMS): $\delta = 12.69$ (C13), 18.13 (C12), 29.95 (C7), 34.10 (C1), 37.73 (C3), 38.24 (*C*H$_2$CO$_2$Me), 39.48 (C2), 50.95 (OMe), 53.39 (C4), 55.63 (OMe), 56.13 (OMe), 59.14 (C6), 63,71 (C11b), 110.0 (C8), 112.8 (C1), 127.5 (C11a), 130.8 (C7a), 148.5 (C10), 148.8 (C9), 172.7 ppm (C=O); $[\alpha]_D^{20} = -57.9$ ($c = 0.60$ in $CHCl_3$). **10b**: ^{1}H NMR (300 MHz, C_6D_6, TMS): $\delta = 0.81$ (t, ^3J(H,H) = 7.5 Hz, 3H; 13-H), 1.00 (m, 1H; 12-H), 1.41–1.52 (m, 3H; 1-H, 12-H, 3-H), 1.80 (m, 1H; CH_2CO$_2$Me), 1.92 (dd, ^2J(H,H) = 15.5 Hz, ^3J(H,H) = 15.5 Hz; 1H, 4-H_{ax}), 2.01 (dd, ^2J(H,H) = 22.0 Hz, ^3J(H,H) = 12.0 Hz; 1H, CH_2CO$_2$Me), 2.35–2.48 (m, 4H; 1-H, 2-H, 6-H, 7-H), 2.77(m; 1H, 6-H), 2.93 (dd, ^2J(H,H) = 15.5 Hz, ^3J(H,H) = 5.5 Hz; 1H, 4-H_{eq}), 3.10–3.14 (m, 2H; 7-H, 11b-H), 3.34 (s, 3H; OMe), 3.42 (s, 3H; OMe), 3.44 (s, 3H; OMe), 6.45, (s, 1H; 8-H), 6.77 ppm (s, 1H; 11-H); ^{13}C NMR (75 MHz, C_6D_6): $\delta = 11.20$ (C13), 23.75 (C12), 30.00 (C7), 38.85 (C1), 38.52 (C3), 38.24 (*C*H$_2$CO$_2$Me), 41.79 (C2), 50.93 (OMe), 52.77 (C4), 55.64 (OMe), 56.00 (OMe), 61.43 (C6), 63,00 (C11b), 110.1 (C8), 112.8 (C1), 127.4 (C11a), 130.8 (C7a), 148.5 (C10), 148.8 (C9), 172.9 ppm (C=O); $[\alpha]_D^{20} = -22.0$ ($c = 1.04$ in $CHCl_3$). **10c**: ^{1}H NMR (300 MHz, C_6D_6, TMS): $\delta = 0.88$ (t, $J = 7.5$ Hz, 3H; 13-H), 1.26 (m, 1H; 3-H), 1.54–1.80 (m, 2H; 12-H), 1.88 (ddd, ^2J(H,H) = 13.5 Hz, ^3J(H,H) = 4.0, 4.0 Hz, 1H; 1-H_{eq}), 2.04 (ddd, ^2J(H,H) = 13.5 Hz, ^3J(H,H) = 10.0, 4.5 Hz, 1H; 1-H_{ax}) 2.22 (m, 1H; 2-H), 2.28–2.45 (m, 3H; CH_2CO$_2$Me, 7-H) 2.57 (t, J = 4.0 Hz, 2H; 4-H_2), 2.53 (dd, ^2J(H,H) = 12.5 Hz, ^3J(H,H) = 4.0 Hz, 1H; 6-H), 2,71 (ddd, ^2J(H,H) = 12.5 Hz, ^3J(H,H) = 6.0, 1.0 Hz, 1H; 6-H), 3.04 (ddd, ^2J(H,H) = 17.0 Hz, ^3J(H,H) = 13.0, 6.5 Hz, 1H; 7-H), 3.43 (m, 1H; 11b-H), 3.39 (s, 3H; OMe), 3.44 (s, 3H; OMe), 6.43, (s, 1H; 8-H), 6.77 ppm (s, 1H; 11-H); ^{13}C NMR (75 MHz, C_6D_6): $\delta = 12.32$ (C13), 25.65 (C12), 28.44 (C7), 32.68 (C1), 33.72 (C2), 37.92 (*C*H$_2$CO$_2$Me), 40.76 (C3), 50.97 (OMe), 53.09 (C6), 54.35 (C4), 55.61 (OMe), 55.65 (OMe), 58.20 (C11b), 109.8 (C8), 112.8 (C11), 127.3 (C11a), 130.1 (C7a), 148.6 (C10), 148.7 (C9), 173.0 ppm (C=O); $[\alpha]_D^{20} = -81.5$ ($c = 0.46$ in $CHCl_3$).

[15] **15d**: ^{1}H NMR (600 MHz, $CDCl_3$, TMS): $\delta = 0.97$ (t, ^3J(H,H) = 7.5 Hz, 3H; 13-H), 1.32–1.43 (m, 2H, 1-H; 12-H), 0.97 (t, ^3J(H,H) = 7.5 Hz, 3H; 13-H), 1.58–1.67 (m, 2H, 1′-H; 3-H), 1.71 (m, 1H; 12-H), 1.83–1.93 (m, 2H; 1-H, 1′-H), 2.08 (m, 1H; 2-H), 2.32 (dd, ^2J(H,H) = 11.5 Hz, ^3J(H,H) = 1.5 Hz, 1H; 4-H), 2.42 (ddd, ^2J(H,H) = 11.5 Hz, ^3J(H,H) = 11.5, 3.5 Hz, 1H; 6-H), 2.55 (m, 1H; 7-H), 2.71 (m, 2H, 4″-H; 7-H), 2.83 (ddd, ^2J(H,H) = 11.5 Hz, ^3J(H,H) = 6.5, 1.5 Hz, 1H; 6-H), 2.95–3.05 (m, 4H; 3″-H, 4-H, 4″-H, 11b-H), 3.23 (m, 1H; 3″-H), 3.78 (s, 3H; OMe), 3.80 (s, 3H; OMe), 3.82 (s, 3H; OMe), 3.83 (s, 3H; OMe), 3.96 (m, 1H; 1″-H), 6.54, 6.55, 6.57, 6.61 ppm (s, 4H; 5″-H, 8-H, 8″-H, 11-H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 12.56$ (C13), 17.45 (C12), 29.30, 29.33 (C4″, C7), 34.82 (C1), 36.61 (C2), 37.30 (C3), 39.83 (C1′), 40.62 (C3″), 52.00 (C2″), 52.95 (C6), 55.72, 55.85, 55.96 (OMe), 58.86 (C4), 63.34 (C11b) 107.8, 109.1, 111.4, 111.7 (C5″, C8, C8″, C11), 126.8, 127.0, 130.6, 131.8 (C4a″, C7a″, C8a, C11a), 146.9, 147.1, 147.1, 147.2 ppm (C6″, C7″, C9, C10); $[\alpha]_D^{20} = -82.3$ ($c = 0.40$ in $CHCl_3$).

