HETEROCYCLES, Vol. 82, No. 2, 2011, pp. 1127 - 1132. © The Japan Institute of Heterocyclic Chemistry
Received, 30th June, 2010, Accepted, 12th August, 2010, Published online, 13th August, 2010
DOI: 10.3987/COM-10-S(E)88

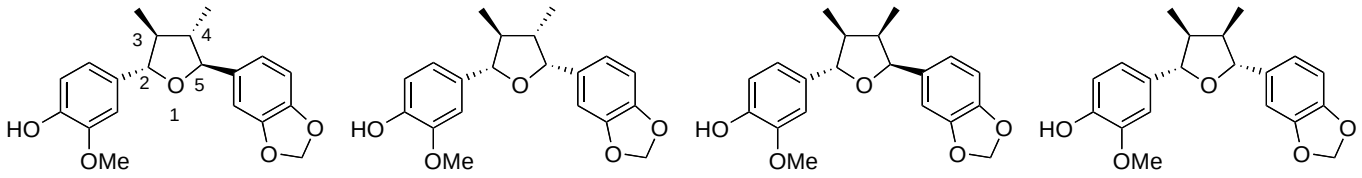
ASYMMETRIC SYNTHESIS OF (+)-MACHILIN F BY UNUSUAL STEREOSELECTIVE MITSUNOBU REACTION

Kenichi Harada, Naoko Kubo, Kazuma Tanabe, Miwa Kubo, Tomoyuki Esumi, Hideaki Hioki, and Yoshiyasu Fukuyama*

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima, 770-8514, Japan
E-mail: fukuyama@ph.bunri-u.ac.jp

Abstract – First synthesis of (+)-machilin F (**1c**) has been achieved in 16 steps as part of systematic synthetic studies on (–)-talaumidin (**1**) and its stereoisomers. The 2,3,4,5-tetrasubstituted tetrahydrofuran with the (2*S*,3*S*,4*R*,5*R*)-configuration has been constructed stereoselectively from diol **14** by Mitsunobu reaction.

Talaumidin (**1**),[1] a 2,5-biaryl-3,4-dimethyltetrahydrofuran neolignan with successive four stereogenic centers, was isolated from Brazilian plant *Aristolochia arcuata* Masters along with a series of 2,5-biaryl-3,4-dimethyltetrahydrofuran type lignans. In addition to this structural feature, **1** not only significantly promotes neurite-outgrowth but also exhibits neuroprotective activity in the primary cultured rat cortical neurons and NGF-differentiated PC12 cells.[2,3] Thus, **1** is expected to be a lead compound for the treatment of neurodegenerative diseases such as Alzheimer's disease. While **1** possesses the four stereogenic centers on a tetrahydrofuran ring, there are the eight diastereomers without their enantiomers.



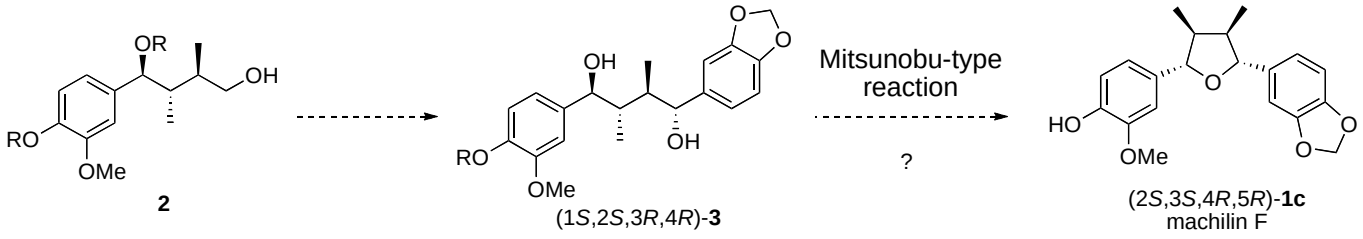
(2*S*,3*S*,4*S*,5*S*)-**1** talaumidin | (2*S*,3*S*,4*S*,5*R*)-**1a** | (2*S*,3*S*,4*R*,5*S*)-**1b** | (2*S*,3*S*,4*R*,5*R*)-**1c** machilin F

Figure 1. Talaumidin and its (2*S*,3*S*)-stereoisomers **1a**-**1c**

Dedicated to Prof. Dr. Albert Eschenmoser on the occasion of his 85th birthday.

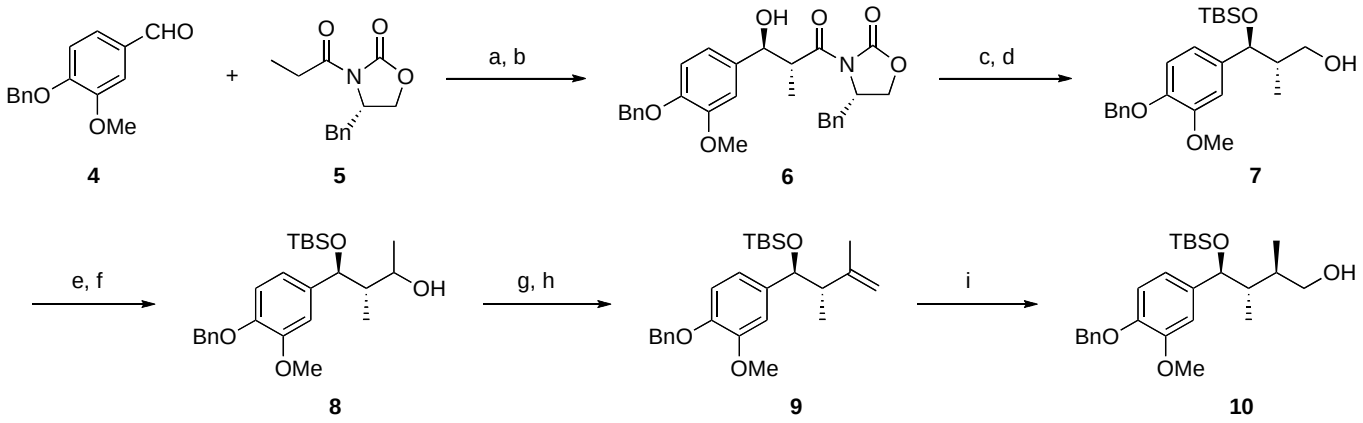
From synthetic and biological points of view, it is desirable to develop a stereoselective approach toward each synthesis of the seven diastereomers, which are specifically intended to compare the neurotrophic activity of **1** and its stereoisomers. In the preceding papers,[4,5] we reported the stereo-controlled syntheses of (–)-talaumidin (**1**) and its stereoisomers (2*S*,3*S*,4*S*,5*R*)-**1a** and (2*S*,3*S*,4*R*,5*S*)-**1b,** but the synthesis of (2*S*,3*S*,4*R*,5*R*)-**1c**, which is the sole remaining (2*S*,3*S*)-series, has not been achieved (Figure 1). As part of our studies on the systematic synthesis of all the stereoisomers of talaumidin, we herein report the efficient synthesis of (2*S*,3*S*,4*R*,5*R*)-**1c** by applying unusual setereoselective Mitsunobu reaction to construct a tetrahydrofuran ring bearing (2*S*,5*R*)-configuration. It should be noted that the stereoisomer **1c** is a natural product, named machilin F[6] and also 7-*epi*-austrobailignan,[7] isolated from *Machilus thunbergii* and *Aristlochia Chilensis*, respectively and no asymmetric synthesis of (2*S*,3*S*,4*R*,5*R*)-series such as **1c** has been reported though a number of syntheses of 2,5-biaryl-3,4-dimethyl tetrahydrofuran lignans were reported. [8-14]

Our synthetic strategy for machilin F (**1c**) is outlined in Scheme 1. An optically active compound **2** is prepared by *anti*-selective Evans aldol reaction and diastereoselective hydroboration according to the synthetic route of **1**.[4,5] (1*S*,2*S*,3*R*,4*R*)-Diol **3** would be derived from **2** by oxidation and Grignard reaction. We envisioned the construction of the tetrahydrofuran ring of the target molecule **1c** from diol **3** through an intramolecular Mitsunobu reaction. This strategy introduces an intriguing question concerning the stereochemical course of its reaction toward benzylic alcohols in **3**.



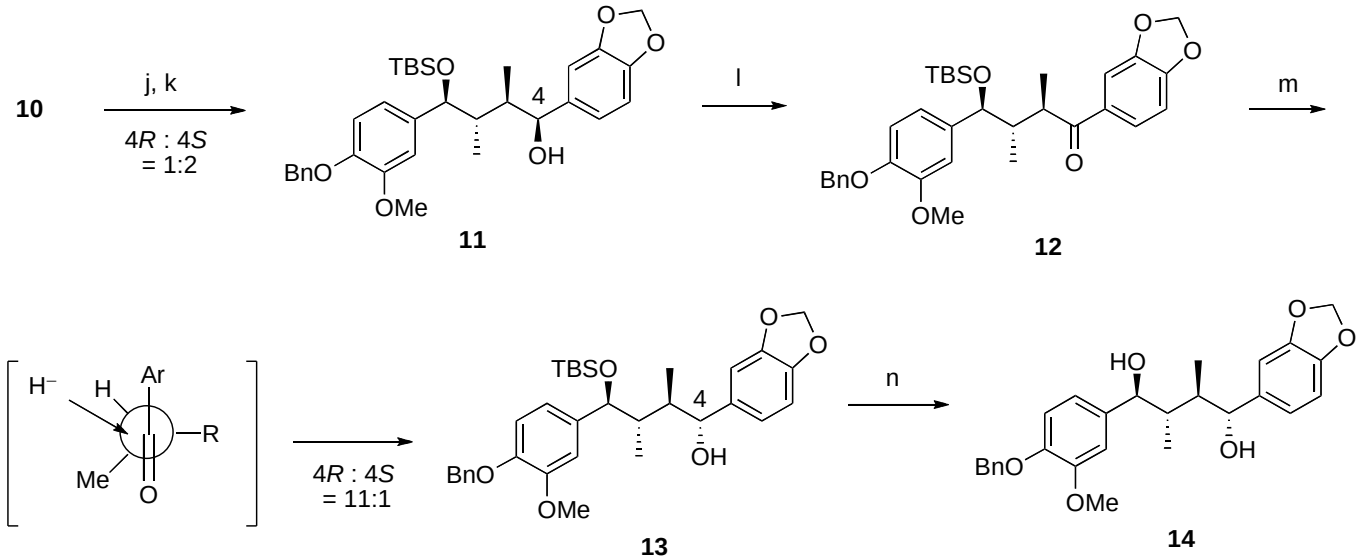
Scheme 1. Synthetic strategy for machilin F

The synthesis of machilin F began with the *anti*-selective Evans aldol reaction[15-18] (Scheme 2). Reaction of 4-benzyloxy-3-methoxybenzaldehyde (**4**) with (+)-4-benzyl-3-propionyloxazolidinone (**5**) catalyzed by 10 mol% $MgCl_2$ in the presence of TMSCl and Et_3N gave the (2*S*,3*S*)-aldol **6** in 86% yield with 98% *de*. The alcohol **7** was obtained from **6** in 91% yield by TBS protection of secondary alcohol followed by reductive removal of the oxazolidinone auxiliary. Swern oxidation of **7** followed by treatment with CH_3MgBr provided secondary alcohol **8** in 89% yield. Swern oxidation of **8** gave the ketone, which was converted to the exo-methylene **9** by Tebbe olefination in 77% yield. The subsequent hydroboration of **9** with 9-BBN generated a new chiral center C-3, giving rise to the alcohol **10** in 71% yield with 99% *de*.[5,19,20]

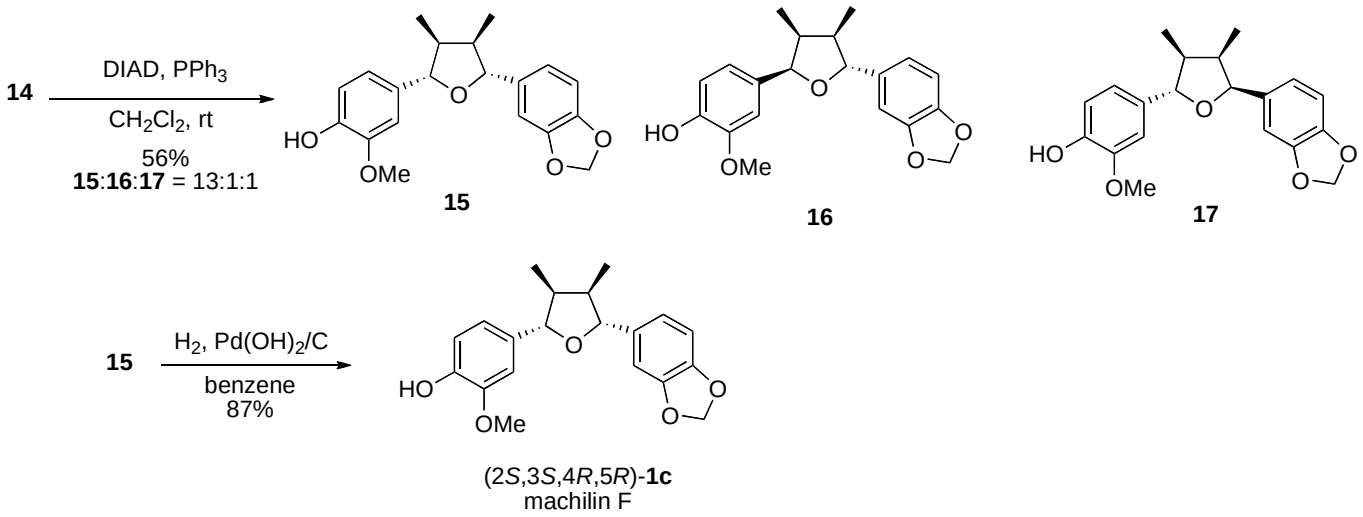


Scheme 2. *Reagents and Conditions*: (a) 10 mol% $MgCl_2$, TMSCl, Et_3N, EtOAc, rt; (b) HF, pyridine, MeCN, rt, 86% in 2 steps, 98% *de*; (c) TBSCl, imidazole, DMF, rt; (d) $LiBH_4$, MeOH, ether, rt, 91% in 2 steps; (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −10 °C; (f) MeMgBr, THF, 0 °C, 89% in 2 steps; (g) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −10 °C; (h) Tebbe reagent, THF, −40 °C, 77% in 2 steps; (i) 9-BBN, THF, 0 °C, then H_2O_2, NaOH, 0 °C, 71%, 99% *de*.

Our next attention was directed toward preparation of (1*S*,4*R*)-diol and the subsequent intramolecular Mitsunobu-type cyclization. Dess-Martin oxidation of **10** gave an aldehyde, which was reacted with 3,4-methylenedioxyphenyl magnesium bromide, giving rise to the undesired diastereomer as the main product (desired 4*R* : undesired 4*S* = 1:2) (Scheme 3). The 4*S* isomer, however, could be readily converted to the necessary 4*R*-configuration with a high selectivity by Dess-Martin oxidation and the subsequent Luche reduction.[9] This stereochemical inversion is rationalized as proceeding through Felkin-Anh fashion.



Scheme 3. *Reagents and Conditions*: (j) Dess-Martin periodinane, CH_2Cl_2, rt; (k) 3,4-methylenedioxyphenyl magnesium bromide, THF, 0 °C, ratio of 4*R* : 4*S* = 1:2; (l) Dess-Martin periodinane, CH_2Cl_2, rt, 71% in 3 steps; (m) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 72%, ratio of 4*R* : 4*S* = 11:1; (n) TBAF, THF, 0 °C, 85%.



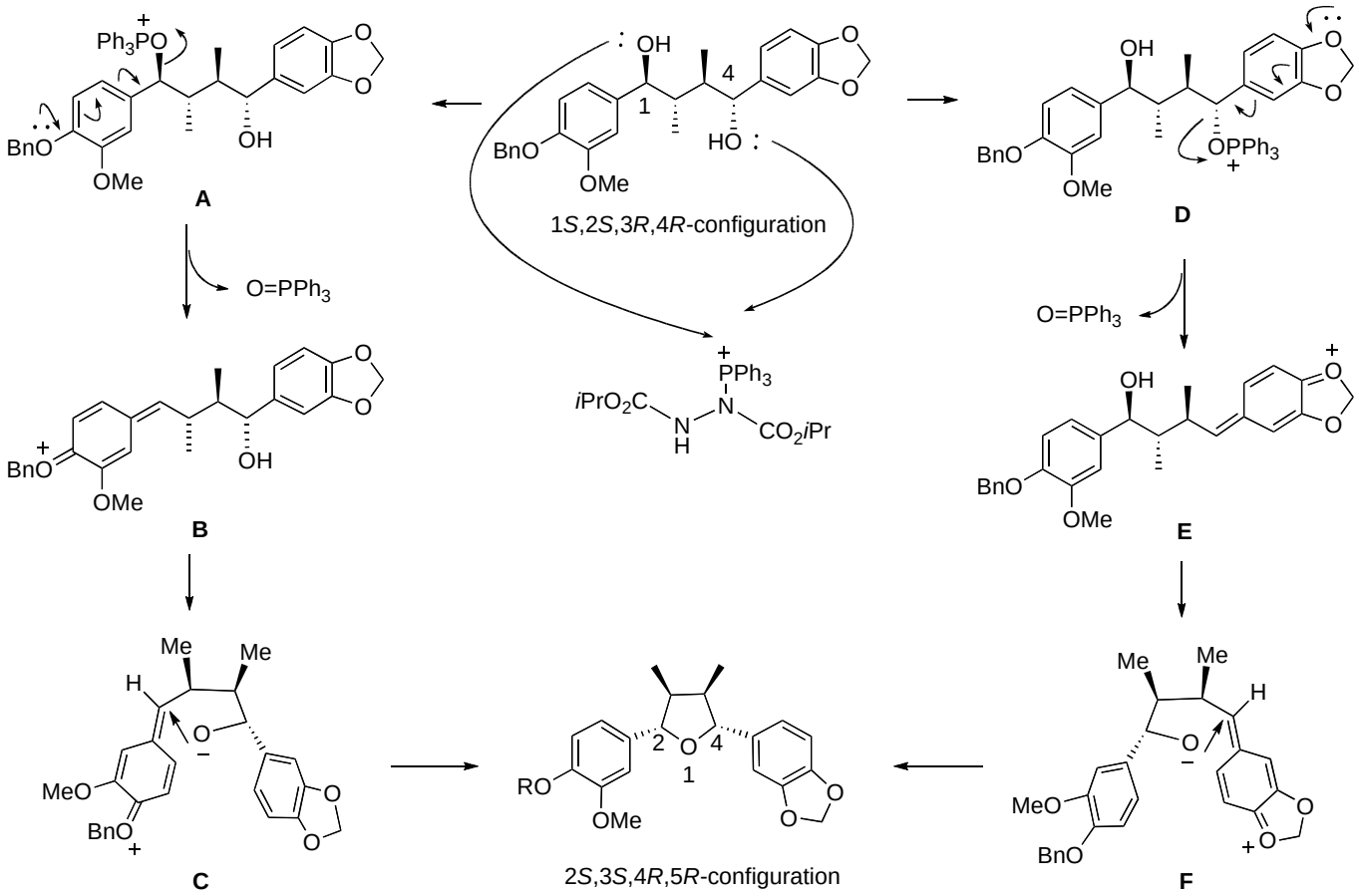
Scheme 4. Mitsunobu reaction of diol **14** and total synthesis of machilin F

The diol **14** was obtained by deprotecting the TBS group in **13** with TBAF in 85% yield. This diol **14**[21] had all configurations necessary for the crucial Mitsunobu-type reaction to construct the tetrahydrofuran ring of **1c** (Scheme 4). Mitsunobu-type cyclization of **14** was carried out under normal conditions, with DIAD and PPh_3 in CH_2Cl_2 at room temperature. *It should be emphasized that our desired product **15** was predominantly produced along with small amounts of diastereomers **16** and **17** (**15**:**16**:**17**=13:1:1) in 56% yield.* It is important to note that major product **15** is the result of a net retention stereochemical process. Finally, removal of the benzyl group with $Pd(OH)_2/C$ in benzene furnished (+)-machilin F, (2*S*,3*S*,4*R*,5*R*)-**1c**, in 87% yield. All the spectroscopic data[22] (^{1}H NMR, ^{13}C NMR, and mass spectra) of the synthetic **1c** were identical with those of natural machilin F.

The surprising stereoselectivity of this Mitsunobu reaction is rationalized as follows: normal Mitsunobu reaction occurs *via* S_N2 inversion mechanism after activation of hydroxy group.[23] In this case, the activated hydroxy group preferentially eliminates over the normal substitution pathway giving rise to quinone methides **B** and **E**, presumably due to the benzylic nature of the hydroxy group [9,24] (Scheme 5). The steric repulsion between an aryl subsutituent and a methyl group results in forcing the active intermediates **B** and **E** to adopt *trans* configurations **C** and **F** to adjacent methyl group.

As results, the cyclization would proceed with net retention of the original configuration at C-1 and C-4. This mechanistic insight can account for the stereoselective formation of the same product **15** with (2*S*,3*S*,4*R*,5*R*)-confiuguration from **A** and **D** even if either a hydroxy group at C-1 or C-4 is activated by the Mitunobu reaction conditions.

In conclusion, we have achieved the first asymmetric synthesis of (+)-machilin F, (2*S*,3*S*,4*R*,5*R*)-**1c**, by applying Mitsunobu reaction to the diol **14**, and thus all (2*S*,3*S*)-series of talaumidin are now prepared for assessment of comparable neurotrophic activity. Further synthetic studies on the remaining four stereoisomers with (2*S*,3*R*)-configuration are now in progress and will be reported in due time.



Scheme 5. The unusual stereoselectivity of Mitsunobu reaction

ACKNOWLEDGEMENTS

We thank Dr. Masami Tanaka and Ms. Yasuko Okamoto for measuring NMR and MS spectra. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and MEXT-Senryaku.

REFERENCES

1. L. M. Vilra, A. Kijioa, A. M. S. Silva, I.-O. Mondranondra, and W. Herz, *Phytochemistry*, 1998, **48**, 1079.
2. H. Zhai, M. Nakatsukasa, Y. Mitsumoto, and Y. Fukuyama, *Planta Med.*, 2004, **70**, 598.
3. H. Zhai, T. Inoue, M. Moriyama, T. Esumi, Y. Mitsumoto, and Y. Fukuyama, *Biol. Pharm. Bull.*, 2005, **28**, 289.
4. Y. Fukuyama, K. Harada, T. Esumi, D. Hojyo, Y. Kujime, N. Kubo, M. Kubo, and H. Hioki, *Heterocycles*, 2008, **76**, 551.
5. T. Esumi, D. Hojyo, H. Zhai, and Y. Fukuyama, *Tetrahedron Lett.*, 2006, **47**, 3979.

6. H. Shimomura, Y. Sashida, and M. Oohara, *Phytochemistry*, 1988, **27**, 634.
7. A. Urzua and L. Presle, *Phytochemistry*, 1993, **34**, 874.
8. S. Hanessian, G. J. Reddy, and N. Chahal, *Org. Lett*., 2006, **8**, 5477.
9. S. Hanessian and G. J. Reddy, *Synlett*, 2007, 475.
10. H. Kim, C. M. Wooten, Y. Park, and J. Hong, *Org. Lett*., 2007, **9**, 3965.
11. K. Matcha and S. Ghosh, *Tetrahedron Lett*., 2008, **49**, 3433.
12. P. Xue, L.-P. Wang, X.-Z. Jiao, Y.-J. Jiang, Q. Xiao, Z.-G. Luo, P. Xie, and X.-T. Liang, *J. Asian Nat. Prod. Res*., 2009, **11**, 281.
13. H. Kim, A. C. Kasper, E. J. Moon, Y. Park, C. M. Wooten, M. W. Dewhirst, and J. Hong, *Org. Lett*., 2009, **11**, 89.
14. C. E. Rye and D. Barker, *Synlett*, 2009, 3315.
15. D. A. Evans, J. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc*., 1991, **113**, 1047.
16. D. A. Evans, J. V. Nelson, and T. T. Taber, *Stereochem*., 1982, **13**, 111.
17. J. R. Gage and D. A. Evans, *Org. Synth*., 1990, **68**, 83.
18. D. A. Evans, J. S. Tedrow, J. T. Shaw, and C. W. Downey, *J. Am. Chem. Soc*., 2002, **124**, 392.
19. K. N. Houk, N. G. Ronda, Y.-D. Wu, J. T. Metz, and M. N. Paddon-Row, *Tetrahedron*, 1984, **40**, 2257.
20. R. S. Coleman and S. R. Gurrala, *Org. Lett*., 2004, **6**, 4025.
21. Data of **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (3H, d, *J* = 6.0 Hz), 0.80 (3H, d, *J* = 6.0 Hz), 2.04-2.11 (2H, m), 3.90 (3H, s), 4.52 (2H, d, *J* = 7.4 Hz), 5.14 (2H, s), 5.94 (2H, s), 6.73-6.91 (6H, m), 7.27-7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 15.1, 41.9, 42.2, 56.0, 71.1, 100.9, 102.1, 107.0, 107.9, 110.1, 113.6, 118.9, 120.1, 127.3, 127.8, 128.5, 137.2, 137.7, 138.7, 146.7, 147.4, 147.7, 149.6; IR (ATR) 1037, 1249, 1506, 2961, 3209 cm^{-1}; EIMS *m/z* (rel. int.) 450 $[M]^+$ (10), 190 (50), 149 (20), 91 (100); HREIMS calcd 450.2043 for $C_{27}H_{30}O_6$, found 450.2068; $[\alpha]^{20}_D$ +14.6 (c 0.18, $CHCl_3$).
22. Data of **1c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (6H, d, *J* = 6.6 Hz), 2.22-2.34 (2H, m), 3.91 (3H, s), 4.45 (1H, d, *J* = 6.4 Hz), 4.46 (1H, d, *J* = 6.7 Hz), 5.57 (1H, s), 5.96 (2H, s), 6.79 (1H, d, *J* = 7.8 Hz), 6.88 (1H, dd, *J* = 7.8, 1.6 Hz), 6.90 (1H, s), 6.94 (1H, d, *J* = 1.6 Hz), 6.97 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 12.9, 44.5, 44.5, 55.9, 87.4, 87.5, 101.0, 106.8, 108.0, 109.0, 114.1, 119.4, 119.9, 134.0, 136.2, 145.0, 146.5, 147.0, 147.8; IR (ATR) 1038, 1247, 1516, 2964, 3481 cm^{-1}; EIMS *m/z* (rel. int.) 342 $[M]^+$ (54), 190 (100), 145 (67); HREIMS calcd 342.1470 for $C_{20}H_{22}O_5$, found 342.1467; $[\alpha]^{20}_D$ +8.4 (c 0.65, $CHCl_3$). Machilin F was reported as optically inactive form.[6]
23. O. Mitsunobu, *Synthesis*, 1981, 1.
24. E. Palomino, A. P. Schaap, and M. J. Heeg, *Tetrahedron Lett*., 1989, **30**, 6797.