Conversion of Ascomycin into its Furano-Isomers

Karl Baumann,* Berndt Oberhauser, Gertrude Strnadt, Hermann Knapp, Gerhard Schulz and Maximilian A. Grassberger

Department of Chemistry and Pharmacology, Novartis Forschungsinstitut, Brunner Strasse 59, A-1235 Vienna, Austria

Fax +43(1)86634 354; E-mail: karl.baumann@pharma.novartis.com

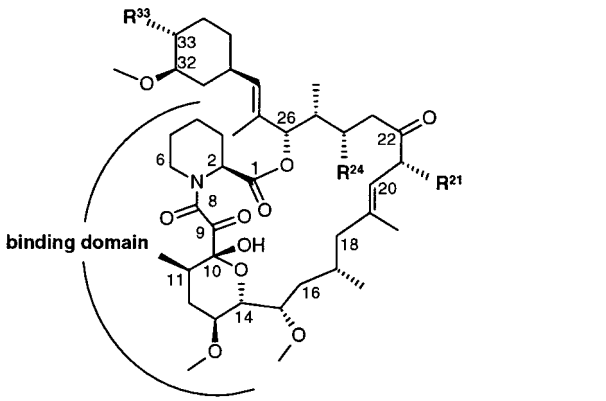
Received 28 January 1999

Dedicated with best wishes to our inspiring teacher Professor A. Eschenmoser, in recognition of his brilliant contributions on the art and science of organic chemistry

Abstract: The high reactivity of the unmasked tricarbonyl segment of ascomycin potentially allows the formation of numerous isomers in the binding domain. In this paper, the synthesis of a novel class of hypothetical equilibrium products of ascomycin is described.

Key words: ascomycin, isomers, binding domain, tricarbonyl

Ascomycin (**1**) is a macrolactam isolated from the fermentation broth of *Streptomyces hygroscopicus var. ascomyceticus*.[1-3] Derivatives of ascomycin have shown interesting anti-inflammatory activities in animal models[4] and in man.[5] SDZ ASM 981 (33-epi-chloro-ascomycin, **2**) is the first representative in clinical development for the treatment of inflammatory skin diseases.[6-10] Ascomycin and related macrolactams feature in the "binding domain" (Fig.1)[11-14] the unusual pattern of three adjacent carbonyl groups (C8-C10), whereby one carbonyl group is involved in hemiketal formation with the secondary hydroxyl group at C-14. The structure shown in Fig.1 is the main isomeric form adopted in organic solution as determined by NMR analysis.[15]



1 Ascomycin (R^{24} = R^{33} = -OH, R^{21} = ethyl)
2 SDZ ASM 981 (R^{24} = -OH, R^{33} = *epi*-Cl, R^{21} = ethyl)
3 24,33-bis-OTBDMS-ascomycin (R^{24} = R^{33} = OTBDMS, R^{21} = ethyl)

Figure 1

Hypothetically, however, the close proximity of the tricarbonyl portion to the hydroxyl group at C-14 allows the potential formation of numerous alternative isomers (Fig. 2). Thus, in solution, the six- and seven membered hemiketals (**A, B**) might be generated via the free tricarbonylform (**T**), followed by unspecific hemiketalization. Considering a preceding enolization at the tricarbonyl unit (**T**-**E**), the formation of the corresponding 11-*epi*-isomers of **A, B** has to be taken into account as well. Furthermore, 1,4-addition of the 14-hydroxyl at the hypothetical enol **E** would result in the formation of the furano-enediol **ED**, which might exist as such or as a set of tautomeric "furano-ascomycins" after tautomerization (**F1, F2,** Fig.2).

Despite the numerous formal equilibrium products that could potentially be formed, only two isomeric hemiketals[16-18] have so far been identified and characterized in solutions of ascomycin or related macrolactams.

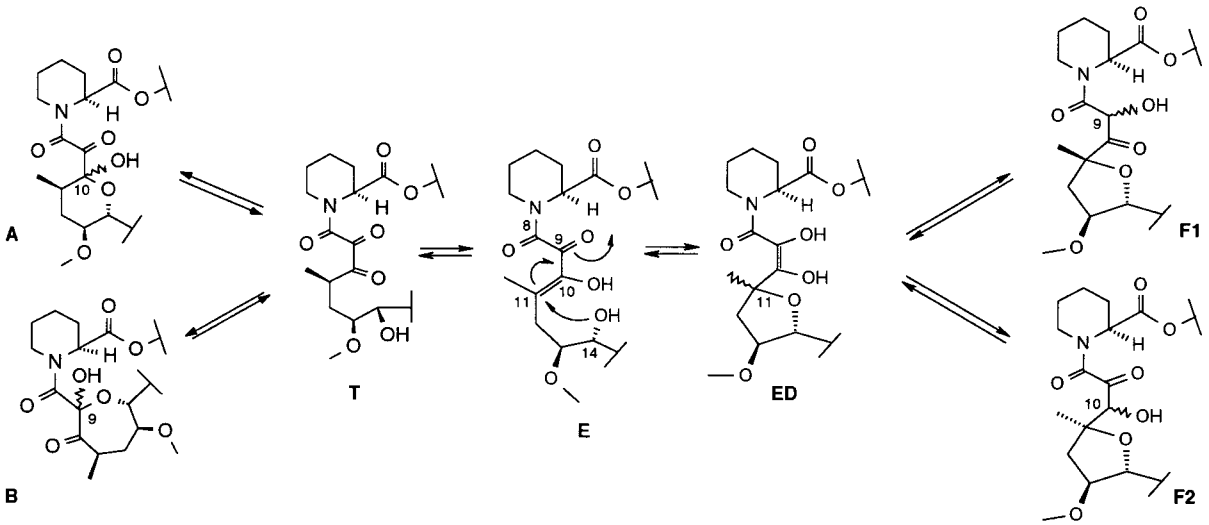
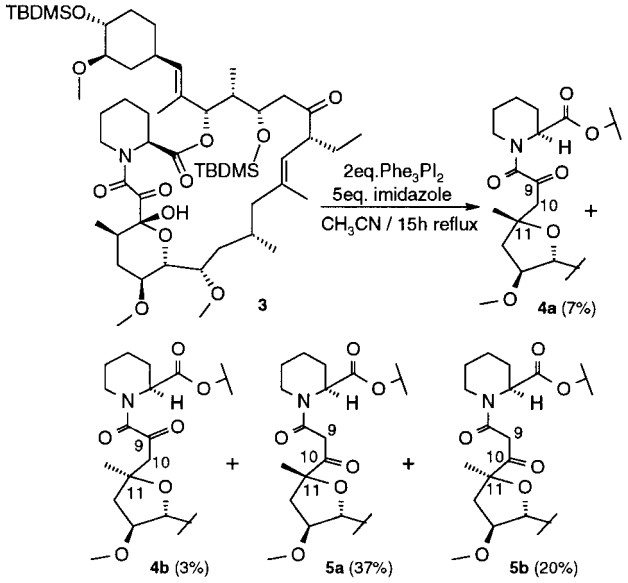


Figure 2 Hypothetical flexibility of the binding domain of ascomycin (only partial structures shown)

Therefore, we aimed not only at the detection, isolation, and characterization of such equilibrium products but also at the synthetic accessibility of further, yet unknown, isomers. In a previous communication, we presented the multigram conversion of ascomycin into its major equilibrium product, the seven-membered hemiketal isomer **B** (compare Fig. 2).[16] Here, we report on the synthesis of four diastereoisomeric furano-ascomycins **8a-d** corresponding to the general structures **F1, F2**. For the formation of the furan ring, an unexpected reaction, occurring at the binding domain of ascomycin, turned out to be helpful: action of diiodo-triphenyl-phosphorane in the presence of imidazole, in refluxing acetonitrile, converted 24,33-bis-OTBDMS-ascomycin[19] **3** into a mixture of the 9- and 10-deoxo-furano-ascomycins **4a,b** and **5a,b,** respectively (Scheme 1).[20]



Scheme 1 (only partial structures shown)

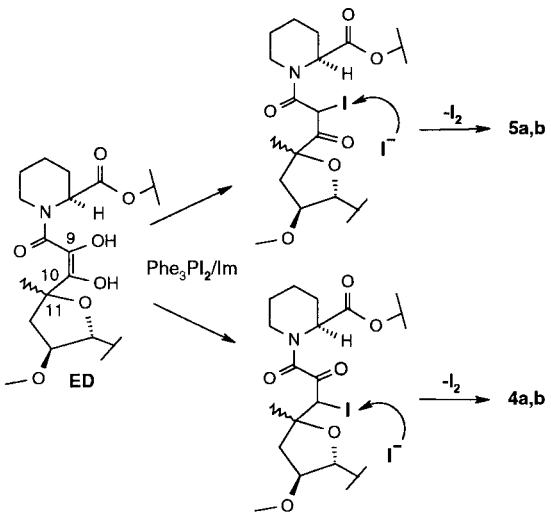
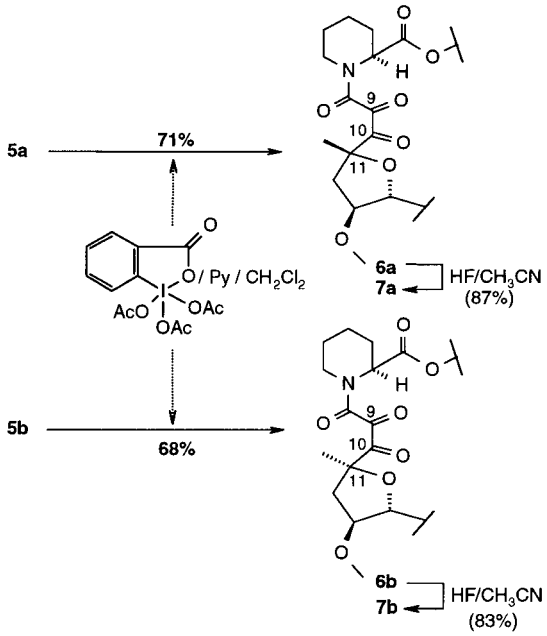


Figure 3 (only partial structures shown)

The formation of **4a,b** and **5a,b** can be explained by assuming (a) an equilibrium between 24,33-bis-OTBDMS-ascomycin **3** and its furano-derivatives (i.e. the enediol **ED**), (b) tautomerization and replacement of either the 9-OH or the 10-OH group by iodine followed by (c) iodide ion mediated dehalogenation (Fig.3).[21]

Transformation of the main products **5a** and **5b** back into the target products (**F1, F2**, Fig.2) required only a few straightforward functional group manipulations (Schemes 2,3). Applying a recently reported methodology,[22] oxidation of the activated methylene group in **5a,b** with Dess-Martin periodinane in the presence of pyridine yielded the yellow tricarbonyl derivatives **6a** and **6b** respectively, which after fluoride-mediated removal of the TBDMS-groups (24,33-OHs), provided the unprotected derivatives **7a** and **7b** in high yields (Scheme 2).[23]

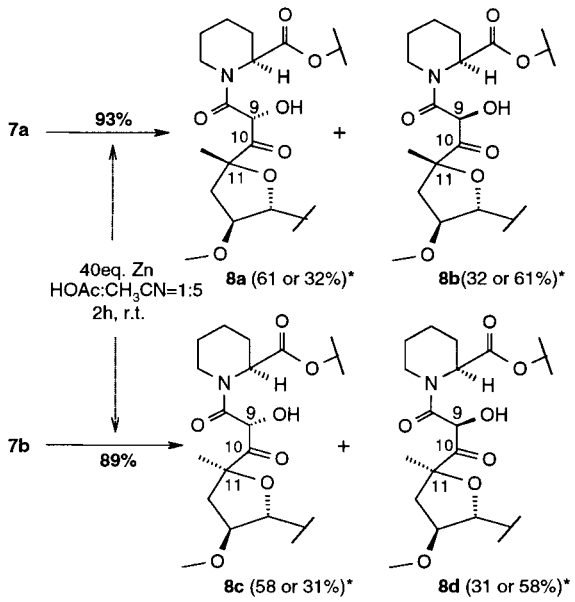


Scheme 2 (only partial structures shown)

Selective reduction of the highly activated 9-carbonyl group of **7a** by treatment with zinc/glacial acetic acid in acetonitrile solution at r.t. provided, after chromatographic separation, the furano-ascomycins **8a** and **8b** in high yield. Starting from **7b**, the 11-*epi*-furano-ascomycins **8c** and **8d** were obtained in an analogous manner (Scheme 3).[24]

Structural assignment, especially of the furano-ascomycins **4a,b** and **5a,b**, was laborious. These compounds exist in $CDCl_3$-solution as a mixture of conformers (*cis vs. trans*-geometry at the amide bond). In addition, an equilibrium between the ketone- and an enol-form is observed in **5a,b**, causing the overlap of four complex sets of signals. However, the carbon-skeleton, as well as the stereochemical configuration at C-11, of both **4a** and **4b** could be elucidated unambiguously from their NMR-data. Although the structures of **5a,b** could be solved, attempts to determine their absolute configuration at C-11 via NMR spectroscopy failed. In this case, the absolute configura-

tion at C-11 could only be assigned indirectly, using the less complex NMR-data sets of the corresponding oxidized derivatives **6a** and **6b**. The absolute configurations at C-9 of **8a-d** are not yet known. However, the 11-*S*-furano-ascomycins[25] **8a** and **8b** differ only with respect to the stereochemical configuration at C-9. The same applies for the 11-*R*-derivatives[26] **8c** and **8d**, as could be shown by equilibration experiments under basic conditions. Thus, treatment of either isolated pure **8a** or **8b** with triethylamine in acetonitrile solution led to a fast epimerization at C-9 generating a mixture of the isomers **8a,b**. Analogous results were obtained starting from the 11-*epi*-isomers **8c,d**. With exception of this equilibration reaction, the isolated pure furano-ascomycins **8a-d** turned out to be remarkably stable towards several conditions. No decomposition at r.t., even after storage for several months could be seen. More importantly, no back-conversion into the parent compound ascomycin in protic or aprotic solutions, under neutral, basic or acidic conditions could be detected. Likewise no formation of **8a-d** was observed in solutions of ascomycin. As a result, no evidence for an equilibration between the furano-ascomycins **8a-d** and the parent compound ascomycin (**1**) could be demonstrated.



Scheme 3 (only partial structures shown)

References and Notes

(1) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T.. *J. Am. Chem. Soc.* **1987**, *109*, 5031.

(2) Hatanaka, H.; Kino, T.; Miyata, S.; Inamura, N.; Kuroda, A.; Goto, T.; Tanaka, H.; Okuhara, M.. *J. Antibiot.* **1988**, *41*, 1592.

(3) Morisaki, M.; Arai, T. *J. Antibiot.* **1992**, *45*, 126.

(4) For a review, see: Stuetz,A.; Grassberger, M.A.; Baumann, K.; Edmunds, A.J.F.; Hiestand, P.: Meingassner, J.G.; Nussbaumer, P.; Schuler, W.; Zenke, G. in *Perspectives in Medicinal Chemistry*, Testa, B.; Kyburz, E,; Fuhrer, W.; Giger, R. (Eds.), Verlag Helv. Chim. Acta, Basle and VCH, Weinheim, **1993**, Chapt. 27, 427-44.

(5) Rappersberger, K.; Meingassner, J. G.; Fialla, R.; Fodinger, D.; Sterniczky, B.; Rauch, S.; Putz, E.; Stuetz, A.; Wolff, K.. *J. Invest. Dermatol.* **1996**, *106*, 701.

(6) Grassberger, M.A.; Baumruker, T.; Enz, A.; Hiestand, P.; Kalthoff, F.; Schuler, W.; Schulz, M.; Werner, F.-J.: Winiski, A.; Wolff, B.; Zenke, G. *Br. J. Dermatol.* in press.

(7) Van Leent, E. J. M.; Graber, M.; Thurston, M.; Wagenaar, A.; Spuls, P. I.; Bos, J. D. *Arch. Dermatol*. **1998**, *134*, 805.

(8) Graul, A.; Castaner, J. *Drugs Future* **1998**, *23*, 508.

(9) Meingassner, J. G.; Grassberger, M.; Fahrngruber, H.; Moore, H. D.; Schuurman, H.; Stuetz, A. *Br. J. Dermatol*. **1997**, *137*, 568.

(10) Paul C., Ho V.C. *Seminars in Cutaneous Medicine and Surgery* **1998**, *17*, 1-5.

(11) Van Duyne, Gregory D.; Standaert, Robert F.; Karplus, P. Andrew; Schreiber, Stuart L.; Clardy, Jon. *Science* **1991**, *252*, 839, and references cited therein.

(12) For a review, see: Grassberger, M. A.; Baumann, K. *Current Opinion in Therapeutic Patents*, **1993**, 931.

(13) Griffith, J. P.; Kim, J. L.; Kim, E. E.; Sintchak, M. D.; Thomson, J. A.; Fitzgibbon, M. J.; Fleming, M. A.; Caron, P. R.; Hsiao, K.; Navia, M. A. *Cell* **1995**, *82*, 507.

(14) Kissinger, C. R.; Parge, H. E.; Knighton, D. R.; Lewis, C. T.; Pelletier, L. A.; Tempczyk, A.; Kalish, V. J.; Tucker, K. D.; Showalter, R. E.; Moomaw, E. W.; Gastinel, L. N.; Habuka, N.; Chen, X.; Maldonado, F.; Barker, J. E.; Bacquet, R.; Villafranca, E. J. *Nature* **1995**, *378*, 641.

(15) Mierke, D. F.; Schmieder, P.; Karuso, P.; Kessler, H. *Helv. Chim. Acta* **1991**, *74*, 1027.

(16) Baumann, K.; Oberhauser, B.; Grassberger, M. A.; Haidl, G.; Schulz, G. *Tetrahedron Lett.* **1995**, *36*, 2231.

(17) Gailliot, F. P.; Natishan, T. K.; Ballard, J. M.; Reamer, R. A.; Kuczynski, D.; McManemin, G. J.; Egan, R. S.; Buckland, B. C. *J. Antibiot*. **1994**, *47*, 806.

(18) Namiki, Y.; Kihara, N.; Koda, S.; Hane, K.; Yasuda, T. *J. Antibiot*. **1993**, *46*, 1149.

(19) Zimmer, R.; Grassberger, M. A.; Baumann, K.; Schulz, G.; Haidl, E.. *Tetrahedron* **1994**, *50*, 13655.

(20) Preparation of **4a,b** and **5a,b**: Iodine (2.49g, 9.8mmol) was added to a solution of triphenylphosphine (2.49g, 9.8mmol) and imidazole (1.67g, 24.5mmol) in 250ml CH_3CN. After 10min at r.t. 24,33-bis-OTBDMS-ascomycin **3** (5.0g, 4.9mmol) was added in one portion and the mixture was allowed to reflux for 15h. After cooling to r.t., the mixture was partitioned between 1N HCl and AcOEt. The organic layer was separated, washed twice with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography over silica gel (gradient: toluene : AcOEt = 9-4 : 1) gave 650mg of a mixture of **3** and **4a,b**, 1.82g (37%, **5a**) and 984mg (20%, **5b**) respectively. Flash chromatography of the mixture of **3** and **4a,b** over silica gel (gradient: CH_2Cl_2 : acetone = 30-15 : 1) provided 70mg (1,4%, starting material **3**), 345mg (7%, **4a**) and 150mg (3%, **4b**), respectively.

(21) Iodide ion catalyzed dehalogenations of 2-halo ketones have been reported, see: Mandal, A. K.; Nijasure, A. M. *Synlett* **1990**, 554.

(22) Batchelor, M. J.; Gillespie, R. J.; Golec, J. M. C.; Hedgecock, C. J. R. *Tetrahedron Lett*. **1993**, *34*, 167.

(23) Preparation of **7a**: Dess-Martin periodinane (2.96g, 7mmol) was added to a solution of **5a** (1.5g , 1mmol) and pyridine (0.8g, 10mmol) in 50ml CH_2Cl_2. After stirring 15 h at r.t., the mixture was concentrated to 15ml. Purification by flash chromatography over silica gel (eluent: n-heptane : AcOEt = 3 : 1) gave **6a** (0.72g, 72%) as yellow foam. 1ml 40w/w % aq.

hydrogen fluoride was added to a solution of **6a** (0.5g, 4.9mmol) in 25ml CH_3CN. After stirring 7 h at r.t., the mixture was partitioned between AcOEt and saturated aq. $NaHCO_3$. The organic layer was separated, washed twice with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (eluent: AcOEt : n-heptane = 3 : 1). The product containing fractions were concentrated, re-dissolved in toluene (in order to remove traces of water) and evaporated to dryness to give **7a** (338mg, 87%) as yellow amorphous powder. Compound **7b** was obtained in the same manner.

(24) Preparation of **8a,b**: zinc powder (1.0g, 15mmol, 40eq.) was added to a solution of **7a** (300mg, 0.38mmol) in 30ml CH_3CN and 6ml glacial AcOH. After stirring for 2 h at r.t. the mixture was filtered and partitioned between excess aq. $NaHCO_3$ and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to dryness. Column chromatography over silica gel (gradient: CH_2Cl_2 : CH_3OH = 50-25 : 1) gave 99mg (32%, **8a** or **8b**) and 189mg (61%, **8b** or **8a**) respectively. The compounds **8c,d** were prepared analogously.

(25) Spectroscopic data of the 11-*R*-compounds **8a** and **8b**: ^{13}C NMR ($CDCl_3$ / 125.77MHz): 211.89 / 211.41 (C-22); 209.82 / 207.56 (C-10); 169.24 / 169.42 (C-1 or C-8); 168.05 / 168.46 (C-8 or C-1); 140.17 / 139.24 (C-19); 132.18 / 132.03 (C-28 or C-29); 130.88 / 131.51 (C-29 or C-28); 123.75 / 123.95 (C-20); 87.35 / 87.86 (C-11); 85.67 / 84.72 (C-14); 84.11 / 84.24 (C-32); 81.61 / 81.65 (C-13); 79.89 / 78.76 (C-15); 78.76 / 79.01 (C-26); 73.97 / 68.37 (C-9); 73.48 / 73.50 (C-33); 70.18 / 68.65 (C-24); 58.73, 57.32, 56.55 / 58.14, 57.27, 56.45 (3x-OMe); 55.108 / 55.13 (C-21); 52.86 / 53.42 (C-2); 46.71 / 48.06 (C-18); 44.41 / 44.86 (C-23); 44.10 / 42.84 (C-6); 41.80 / 42.17 (C-12); 40.48 / 38.97 (C-25); 37.12 / 35.47 (C-16); 34.93 / 34.95 (C-30); 34.69 / 34.50 (C-31); 31.17 / 31.25 (C-34); 30.53 / 30.39 (C-35); 26.86 / 26.98 (C-17); 26.44 / 25.78 (C-5 or C-3); 25.44 / 24.05 (C-3 or C-5); 24.98 / 22.96 (11-CH_3); 23.57 / 23.58 (C-36); 21.36 / 21.22 (C-4); 20.51 / 20.34 (17-CH_3); 16.38 / 15.55 (19-CH_3); 14.01 / 12.90 (28-CH_3); 11.63 / 11.63 (C-37); 10.31 / 8.98 (25-CH_3).

(26) Spectroscopic data of the 11-*S*-compounds **8c** and **8d**:
8c or **8d**; (mixture of rotamers: *E*-amide:*Z*-amide = 5:4) ^{13}C NMR ($CDCl_3$ / 125.77 MHz, d in ppm of the *E* / *Z*-amide): 213.28 / 211.53 (C-22); 210.48 / 208.78 (C-10); 169.73/ 169.44 (C-1 or C-8); 166.52 /.169.13 (C-8 or C-1); 137.08 / 138.63 (C-19); 131.98 / 131.38 (C-28 or C-29); 128.82 / 131.17 (C-29 or C-28); 124.25 / 123.60 (C-20); 89.35 / 89.40 (C-11); 85.49 / 86.18 (C-14); 84.17 / 84.15 (C-32); 83.05 / 83.58 (C-13); 79.26 / 80.6 (C-15); 76.90 / 80.60 (C-26); 78.44 / 73.84 (C-9); 73.52 / 73.51 (C-33); 69.79 / 67.94 (C-24); 57.5, 56.83, 56.32 / 56.58, 46.47, 56.43 (3x-OMe); 53,58 / 54.65 (C-21); 56.41 / 53.54 (C-2); 48.37 / 48.02 (C-18); 45.01 / 45.21 (C-23); 39.56 / 42.88 (C-6); 40.72 / 40.82 (C-12); 39.60 / 39.38 (C-25); 33.10 / 35.64 (C-16); 34.92 / 34.92 (C-30); 34.82 / 34.53 (C-31); 31.19 / 31.19 (C-34); 30.71 / 30.51 (C-35); 27.37 / 28.49 (C-17); 27.52 / 25.63 (C-3); 24.70 / 25.85 (11-CH_3); 21.21 / 20.91 (C-4); 20.21 / 20.91 (17-CH_3); 16.59 / 16.98 (19-CH_3); 14.37 / 13.03 (28-CH_3); 11.48 / 11.61 (C-37); 9.82 / 9.10 (25-CH_3).
8d or **8c**; ^{13}C NMR ($CDCl_3$ / 125.77MHz): 212.70 / 212.46 (C-22./ C-10); 169.73 / 168.32 (C-1 / C-8); 138.59 (C-19); 131.47 (C-28); 131.05 (C-29); 123.67 (C-20); 89.42 (C-11); 87.50 (C-14); 84.19 (C-32); 83.18 (C-13); 79.54 (C-15); 72.96 (C-26); 79.33 (C-9); 73.51 (C-33); 68.60 (C-24); 58.17, 56.48, 55.16 (3x-Ome); 55.16 (C21); 51.97 (C-2); 46.57 (C-18); 43.87 (C-23); 44.14 (C-6); 43.25 (C-12); 39.33 (C-25); 35.56 (C-16); 34.96 (C-30); 34.64 (C-31); 31.21 (C-34); 30.55 (C-35); 26.86 / 28.36 (C-17); 25.43 (C-5); 25.44 / 26.38 (C-3); 24.43 (11-CH_3); 23.80 (C-36); 20.95 (C-4); 21.07 (17-CH_3); 17.76 (19-CH_3); 13.46 (28-CH_3); 11.79 (C-37); 9.75 (25-CH_3).

Article Identifier:
1437-2096,E;1999,0,S1,0877,0880,ftx,en;W03999ST.pdf