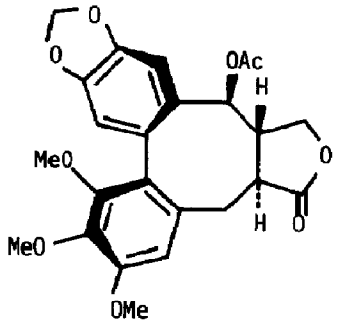
Tetrahedron Letters Vol. 21, pp 2973 - 2976 0040-4039/80/0729-2973$02.00/0

FIRST ASYMMETRIC TOTAL SYNTHESIS OF (+)-STEGANACIN DETERMINATION OF ABSOLUTE STEREOCHEMISTRY

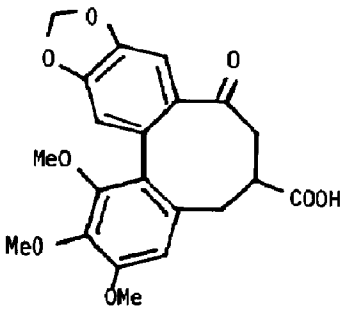
Kiyoshi Tomioka, Tsuneo Ishiguro, and Kenji Koga*
Faculty of Pharmaceutical Sciences, University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113, Japan

Summary: (+)-Steganacin was synthesized in a new and highly specific asymmetric pathway based on the novel application of chiral γ-lactone as a chiral synthon. By this synthesis the absolute stereochemistry of natural (-)-steganacin could be determined in unequivocal way.

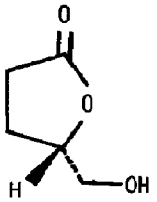
Over the last few years considerable efforts have been devoted on the total synthesis of the antileukemic lignan lactone steganacin whose probable absolute stereochemistry shown in 1 had bee determined by direct X-ray crystallographic analysis of episteganol.[1,2] Successuful syntheses reported to date all include racemic keto-acid (2) as a common intermediate leading to racemic 1.[3] As a consequence of our studies directed toward the asymmetric total synthesis of the anti-leukemic lignan lactones based on the novel application of chiral γ-lactone (3) easily available from L-glutamic acid as a chiral synthon,[4] we wish to describe here the first and highly efficier asymmetric total synthesis of (+)-steganacin (1) not having 2 as an intermediate and as a result of it the correction of absolute stereochemistry of natural (-)-steganacin.



1



2



3

Present total synthesis of (+)-1 includes the highly specific asymmetric 1,4-addition reaction of chiral butenolide (6) leading to 7 and also positional- and stereo-selective introduc tion of acetoxy function onto (+)-stegane (15) leading directly to the target lignan (+)-1 as the key steps as shown in Scheme.

Previously we reported the stereoselective 1,4-addition reaction using benzyl ether instead of trityl ether (6) giving 98% stereoselectivity.[4d] Further improvement was achieved this time

using chiral butenolide (6) having more bulky trityl ether group. Optically pure 6 (mp 153-154°, $[\alpha]_D^{20}$ -95.9°(c=1.03, $CHCl_3$)) was conveniently synthesized from 4 (mp 150°, $[\alpha]_D^{20}$ +28.6°(c=1.05, $CHCl_3$)) in 65% overall yield as follows; treatment of 4 with LDA, then PhSeBr in THF gave 5, which was oxidized with $NaIO_4$ in the presence of catalytic amount of 18-crown-6 in AcOEt-water two phase system at 50° to give 6.[5,6] 6 was then successfully converted to optically pure crystalline 9 (mp 119-120°, $[\alpha]_D^{20}$ +26.7°(c=0.998, $CHCl_3$)) in 65% yield without any purification of each intermediates (7,8) as follows; 1,4-addition reaction of 6 with lithiated trimethoxybenzaldehyde dithioacetal in THF at -78° gave (+)-7, Raney-Nickel desulfurization of (+)-7 in refluxing EtOH gave 8 which was detritylated in conc.HCl-MeOH (1:99) to give 9. Any other stereoisomer of 9 could not be detected. This means that 1,4-addition reaction of 6 with above nucleophile proceeded with complete stereoselection[7] and also without base induced racemization of 6[8]. Treatment of dianion of 9 (2eq.LDA in THF at -78°) with piperonyl bromide gave rise to 10 ($[\alpha]_D^{20}$ +62.6°(c=1.45, EtOH)) in 62% yield.[4d] 10 was converted to (-)-isostegane (14) (mp 169-170° $[\alpha]_D^{23}$ -158°(c=0.735, $CHCl_3$)) in 37% overall yield by the previously reported lactone carbonyl transposition procedure[4d] via (+)-11, (+)-12, and (+)-13 ($LiAlH_4$ reduction, $NaIO_4$ oxidative cleavage of diol to remove original chiral center, Collins oxidation, then VOF_3 nonphenolic oxidative coupling[9]).

Thermal isomerization of (-)-14[4b] was effectively carried out (neat, 195°, 4h) giving selectively, after purification using Waters LC-500 instrument (PrepPAK-500/SILICA, PhH-AcOEt (20:1), 100 ml/min), optically pure (+)-stegane (15) $[\alpha]_D^{23}$ +196°(c=0.52, $CHCl_3$)) in quantitative yield (based on the consumed (-)-14). NMR and tlc behavior of this (+)-15 were indistinguishable from those of racemic 15 synthesized previously by us.[4b]

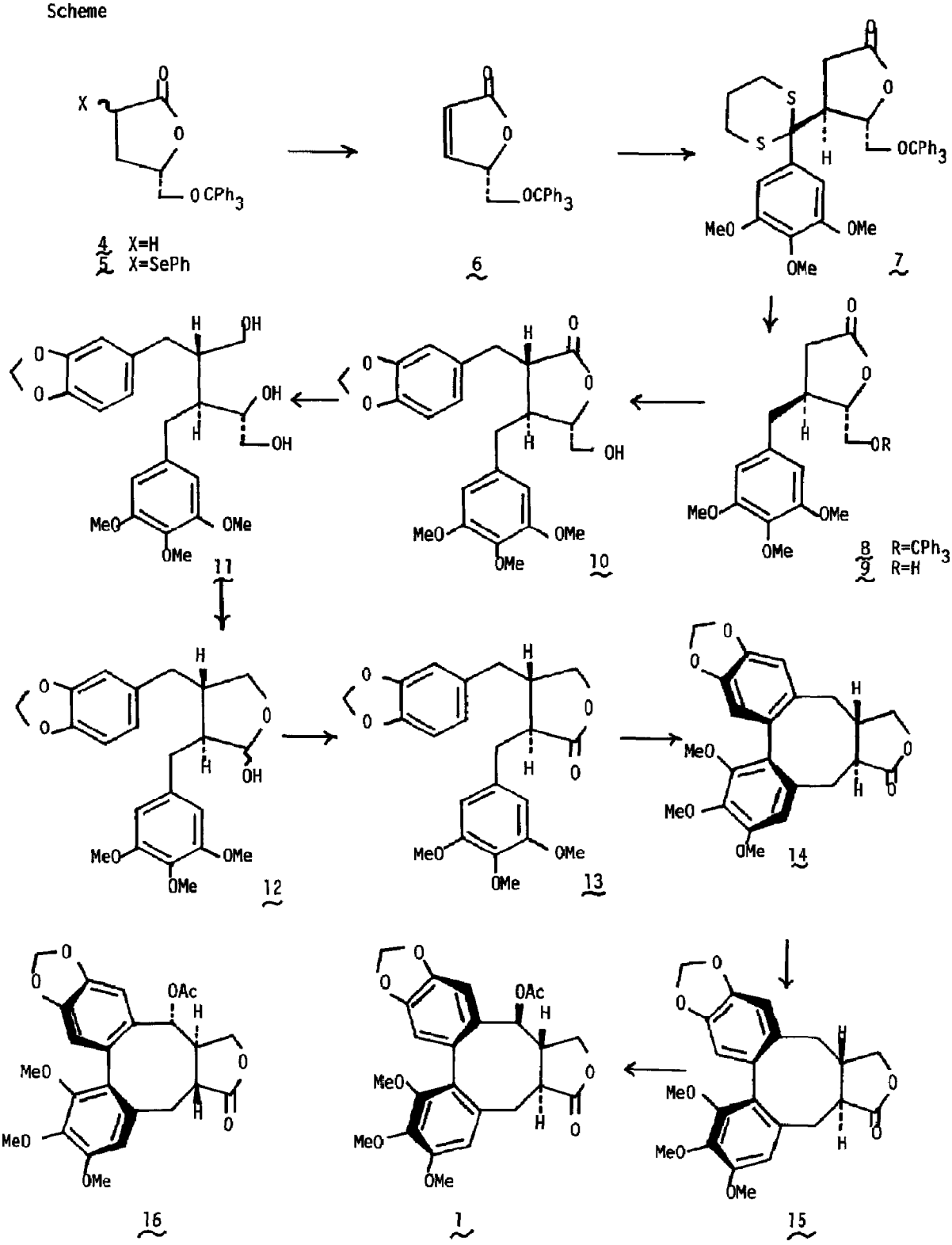
To complete our synthetic scheme the acetoxy function should be introduced selectively in positional- and stereochemical- sense onto (+)-stegane (15). Assuming that selective oxidation of benzylic position could be possible in such case that carbon-hydrogen bond to be oxidized were in perpendicular situation to the plane of aromatic ring, it could be speculated from Dreiding model analysis of (+)-15 that desired position among two benzylic positions could be selectively oxidizable and product should be steganacine.[10]

In fact DDQ oxidation of (+)-15 in AcOH at 70-80° for 50h under argon atmosphere afforded successfully and directly (+)-steganacin (1) ($[\alpha]_D^{23}$ +135°(c=0.70, $CHCl_3$); PMR ($CDCl_3$) δ 1.90(3H, s), 3.73(3H,s), 3.87(3H,s), 3.91(3H,s), 5.82(1H,d,J=10Hz), 6.03(2H,s), 6.45(1H,s), 6.60(1H,s), 6.91(1H,s); IR ($CHCl_3$) 1774, 1734, 1600 cm^{-1}) as a major product in 11% yield.[11] Spectral data (PMR, IR, MASS) and tlc behavior (SiO_2/ PhH, C_6H_{12}-Et_2O (1:1), AcOEt-PhH (1:4), Et_2O-PhH (1:4), $CHCl_3$, $CHCl_3$-Et_2O (10:1)) of this synthetic (+)-1 were in good agreement with those of authentic natural (-)-steganacin and also synthetic racemic steganacin.[12]

It is important to attract attention here that to our surprise present synthetic optically pure steganacin (1) whose absolute stereochemistry is unequivocal based on the present asymmetric synthetic pathway has the opposite sign of optical rotation value to natural steganacin ($[\alpha]_D^{23}$ -114°(c=0.74, $CHCl_3$)).[1] It was concluded from this fact that the absolute stereochemistry of natural antileukemic steganacin presumed as 1 by direct X-ray crystallographic analysis[1] should be corrected to be 16 (an antipode of 1).

Since we have succeeded in the asymmetric synthesis of antipode of 13 starting from 3,[4c]

Scheme


X
OCPh3
4 X=H
5 X=SePh
6
S
S
H
OCPh3
MeO
OMe
OMe
7
OR
8 R=CPh3
9 R=H
10
OH
11
12
13
14
OAc
15
16
1

present successful synthesis of (+)-1 constitutes formal synthesis of natural steganacin (16).

Further synthetic studies based on the novel application of chiral γ-lactone (3) as a chiral synthon are now in progress in our laboratory.

Acknowledgement

The authors are delightful to express their thanks to professors, A. T. Sneden (Verginia Commonwealth University) for natural steganacin and its spectra, A. S. Kende (The University of Rochester), R. A. Raphael (University Chemical Laboratory), and F. E. Ziegler (Yale University) for synthetic steganacin and its spectra.

References and Notes

1. S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, and R. F. Bryan, J. Am. Chem. Soc., 95, 1335(1973).
2. R. W. Wang, L. I. Rebhun, and S. M. Kupchan, Cancer Res., 37, 3071(1977).
3. a) A. S. Kende and L. S. Liebeskind, J. Am. Chem. Soc., 98, 267(1976), b) D. Becker, L. R. Hughes, and R. A. Raphael, J. Chem. Soc. Perkin 1, 1674(1977), E. R. Larson and R. A. Raphael, Tetrahedron Letters, 5041(1979), c) G. R. Krow, K. M. Damodaran, E. Michener, R. Wolf, and J. Guare, J. Org. Chem. 43, 3950(1978), d) F. E. Ziegler, I. Chliwner, K. W. Fowler, S. J. Kanfer, S. J. Kuo, and N. D. Sinha, J. Am. Chem. Soc., 102, 790(1980), e) E. Brown, R. Dhal, and J-P. Robin, Tetrahedron Letters, 733(1979).
4. a) K. Tomioka, H. Mizuguchi, and K. Koga, Tetrahedron Letters, 4687(1978), b) K. Tomioka, H. Mizuguchi, and K. Koga, Tetrahedron Letters, 1409(1979), c) K. Tomioka and K. Koga, Tetrahedron Letters, 3315(1979), d) K. Tomioka, T. Ishiguro, and K. Koga, J. Chem. Soc. Chem. Comm., 652(1979), e) K. Tomioka and K. Koga, Heterocycles, 12, 1523(1979).
5. Satisfactory analytical and spectral data were obtained for all compounds.
6. Because of unstability of 6 in THF-water system, described two phase system was applied. Addition of crown ether was found to accelerate reaction rate.
7. Similar stereoselectivity has been reported in (±)-avenaciolide synthesis. J. L. Herrman, M. H. Berger, and R. H. Schlessinger, J. Am. Chem. Soc., 101, 1544(1979).
8. Facile proton abstruction from butenolide system by base has been reported. G. A. Krau, and B. Roth, Tetrahedron Letters, 3129(1977).
9. Conversion of (±)-13 into (±)-14 has been reported. R. F. Damon, R. H. Schlessinger, and J. F. Blount, J. Org. Chem., 41, 3772(1976).
10. (±)-Isostegane was attempted to oxidize under the same condition described in the text not to give any acetoxy functionalized product.
11. Other acetoxy functionalized compounds were detected. Detail of this oxidation reaction will be published in the near future.
12. (±)-Stegane was also oxidized into (±)-steganacin. Melting point and mixed melting point were in good agreement with authentic racemic steganacin.

(Received in Japan 30 April 1980)