Pergamon

Tetrahedron Letters, Vol. 38, No. 6, pp. 1001-1004, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02481-1

Asymmetric Synthesis of the C(18)-C(24) Unit of Lasonolide A

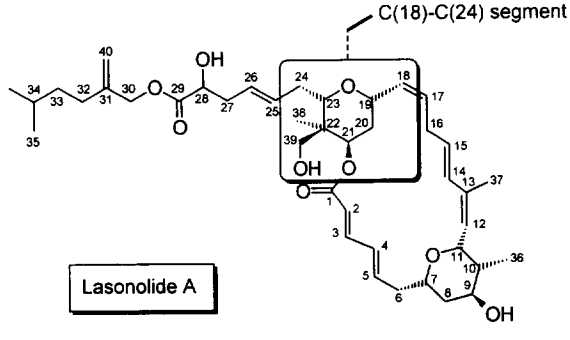
Marc Nowakowski* and H. M. R. Hoffmann*

Department of Organic Chemistry, University of Hannover, Schneiderberg 1 B, 30167 Hannover, Germany

Abstract: The C(18)-C(24) segment of lasonolide A has been prepared with complete chemodifferentiation of functionality. © 1997, Elsevier Science Ltd. All rights reserved.

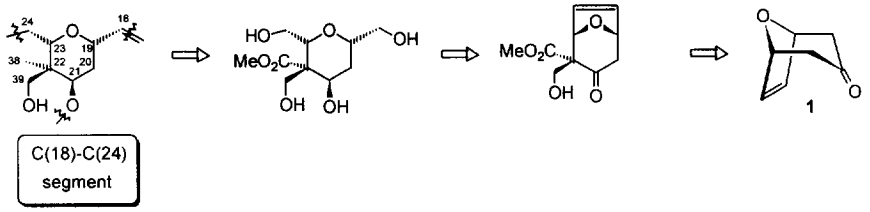
Lasonolide A is a novel macrolide which has recently been isolated and identified by McConnell et al.[1] from a Caribbean marine sponge, *Forcepia sponge*. It has been shown to exhibit potent *in vitro* antineoplastic activity against human A-549 lung carcinoma cells and inhibits cell adhesion in an assay for detecting signal transduction agents. Important structural features are the 20-membered macrocycle which incorporates two tetrahydropyran units. Of a total of nine stereocentres four centres are located on the C(18)-C(24) unit. An asymmetric synthesis of this fragment also presents the challenge of constructing a quaternary centre at C(22) within a densely functionalized segment. We here describe the short assembly of the C(18)-C(24) segment from readily available materials.

Scheme 1



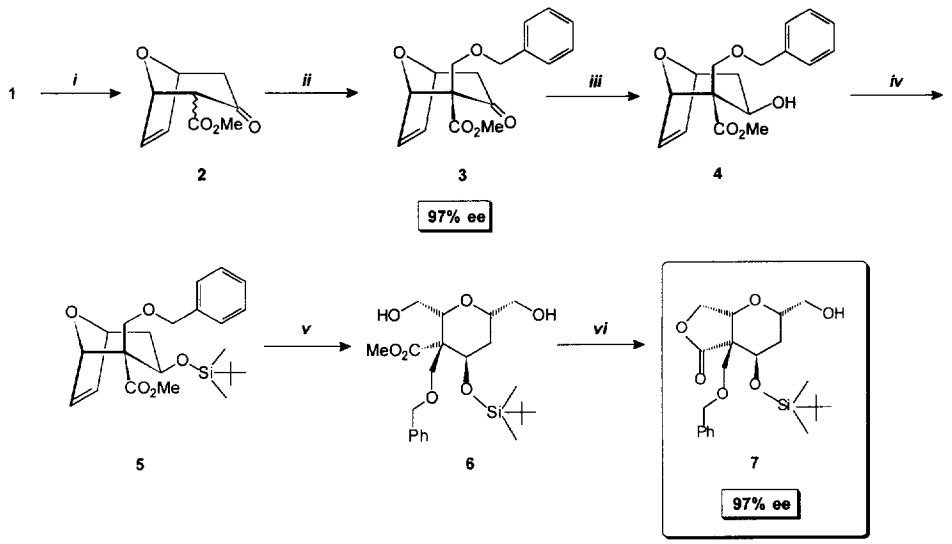
Our retrosynthetic analysis is outlined in Scheme 2. As starting material we envisaged unsaturated oxa-bicyclic ketone **1** which has to be desymmetrized and fitted with a quaternary carbon centre. Remaining steps include stereoselective reduction of the carbonyl group, ozonolytic cleavage of the etheno bridge, reduction and differentiation of the resulting hydroxymethyl groups.

Scheme 2



The individual steps leading to the C(18)-C(24) segment are shown in Scheme 3.

Scheme 3



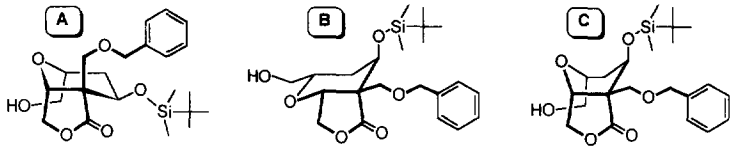
(i) racemic: LiHMDS, TMEDA, $NCCO_2Me$, THF, −78°C, 78%; *(i) asymmetric:* (-)-bis[(*S*)-1-phenylethyl]amidolithium, LiCl, $NCCO_2Me$, THF, −94°C, 71%, 97% ee; *(ii)* NaH, $ClCH_2OBn$, dioxane, 0°C/r.t., 53% (*racemic*), 33% (*asymmetric*); *(iii)* $NaBH_4$, $CeCl_3$, MeOH/EtOH (4:1), −78°C, 36% + 32% α-epimer; *(iv)* TBDSOTf, lutidine, CH_2Cl_2, 0°C/r.t., 94%; *(v)* O_3, $MeOH/CH_2Cl_2$ (1:1), −78°C then $NaBH_4$ (EtOH), −30°C, 87%; *(vi)* imidazole, CH_3CN, 100°C, 76% (*racemic*), 48% (*asymmetric*).

Asymmetric deprotonation[2] of prochiral bicyclic ketone **1** generated a chiral lithium enolate which was C-acylated using methyl cyanoformate MeO_2C-CN. The standard and potentially competing O-acylation was not observed with the Mander reagent.[3] β-Ketoester **2** was deprotonated and treated with benzyloxymethyl chloride to introduce the required axial hydroxymethyl group in protected form and with 100% diastereoselectivity in a substrate-controlled reaction. The enantiomeric purity of the desymmetrized intermediate **3** was determined to a value of 97% ee by ^1H NMR in the presence of (+)-$Eu(hfc)_3$.[4] Reduction of the ketone group under Luche conditions[5] afforded β-configurated alcohol **4**,[6] which was silylated with TBDSOTf to provide protected alcohol **5**. Ozonolysis and immediate reductive work up with sodium borohydride afforded diol **6**. The synthesis was completed by a lactonization (**6** → **7**), which provided the necessary chemodifferentiation of the two hydroxymethyl groups in **6**. Thus, the methoxycarbonyl group

activates not only carbon atom C(22) towards a regio- and stereoselective construction of the stereogenic quaternary centre,[7] but also serves as an anchor for the lactonization in the final step.

In order to elucidate the semirigid structure of the *cis*-fused bicyclic lactone **7** and to investigate the relative configuration of the four chiral centres, we performed NOE experiments. A priori, three conformations can be envisaged for **7**, two 6-membered chair conformations (**A**, **B**) and one 6-membered boat conformation (**C**) (Scheme 4).

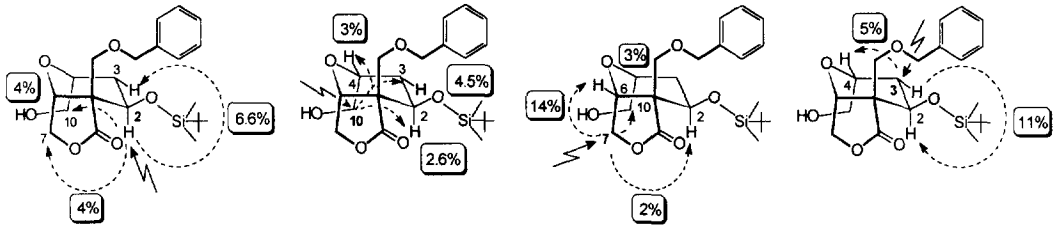
Scheme 4



7

Bidirectional NOE's showed the important interactions marked in Scheme 5. In fact, the assigned relative stereochemistry is confirmed. With respect to conformation analysis, the comparatively bulky $^{t}BuMe_2SiO$ group in **7** prefers to adopt the equatorial position which is only present in chair conformation **A**.

Scheme 5



7 [A]

In summary, our synthesis of the C(18)-C(24) segment of lasonolide A proceeds with high chiral efficiency. In 6 steps the required 4 chiral centres, including a quaternary centre, are correctly assembled, *i.e.* only 1.5 steps per stereogenic centre.[8] A key step is the Simpkins-Koga asymmetric deprotonation of potentially sensitive 8-oxabicyclo[3.2.1]oct-6-en-3-one, which proceeds with high enantiomeric excess (97%) provided the reaction is carried out at −94 °C instead of −78 °C and in the presence of LiCl.[9] Furthermore, the C-*acylation* of the chiral lithium enolate using a sp^2-hybridized electrophile has the advantage over C-alkylation of higher yield[10] and a synthetically flexible β-ketoester is generated.[13] The strategy outlined is versatile and has potential for constructing other C-glycosides and sugar mimics, which occur in a variety of bioactive compounds and marine natural products.

REFERENCES AND NOTES

* To whom correspondence should be addressed: Tel: (511) 762-4611. Fax: (511) 762-3011. E-mail: hoffmann@mbox.oci.uni-hannover.de.

♦ New address: BAYER AG, PH-TO-VEC Process Development Laboratories Pharma, D-42117 Wuppertal, Germany

1. Horton, P. A.; Koehn, F. E.; Longley, R. E.; McConnell, O. J. *J. Am. Chem. Soc.* **1994**, *116*, 6015.
2. a) Simpkins, N. S. *J. Chem. Soc. Chem. Commun.* **1986**, 88. b) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543. c) Cain, C. M.; Simpkins, N. S. *Tetrahedron Lett.* **1987**, *18*, 3723. d) Cox, P. J.; Simpkins, N. S. *Synlett* **1991**, 321. e) Bunn, B. J.; Simpkins, N. S. *J. Org.Chem.* **1993**, *58*, 533. f) Koga, K. *Pure Appl. Chem.* **1994**, *66*, 1487. g) Simpkins, N. S. *Pure Appl. Chem.* **1996**, *68*, 691. h) Sugasawa, K., Shindo, M.; Noguchi, H.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 7377. Catalytic asymmetric alkylation. See: Imai, M.; Hagihara, H.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829.
3. Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
4. Absolute configuration deduced from related oxacycles. See: a) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymm.* **1991**, *2*, 1. b) Bunn, B. J.; Simpkins, N. S.; Spavold, Z.; Crimmin, M. J. *J. Chem. Soc. Perkin Trans. 1* **1993**, 3113 and ref. 2d).
5. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
6. No attempts to recycle the α-configurated alcohol **4**-α, e. g. by back oxidation to ketone **3** or by Mitsunobu inversion were made at this stage.
7. Martin, S.F. *Tetrahedron* **1980**, *36*, 419; Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.
8. Currently, *four* steps and even more per stereogenic centre are not uncommon in total synthesis of complex marine natural products. See: Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041 and references cited therein.
9. Addition of lithium salts for the enhancement of enantioselectivity. See: a) Murakata, M.; Nakajima, M.; Koga, K. *J. Chem. Soc. Chem. Commun.* **1990**, 1657. b) Majewski, M.; Lazny, R.; Nowak, P. *Tetrahedron Lett.* **1995**, *31*, 5465. c) Majewski, M.; Lazny, R. *Tetrahedron Lett.* **1994**, *35*, 3653. Previously, 8-oxabicyclo[3.2.1]octan-3-one, which is obtained from **1** by catalytic hydrogenation and is more stable, was desymmetrized with a chiral lithium amide base (ca. 78%, 82% e.e.; see ref. 2g).
10. sp^3-hybridized electrophiles such as methyl halides and also benzyl halides give a poor yield of C-alkylation, which generally does not exceed 35-40%; cf. Rubinger, M. M. M.; Mann, J.; Drew, M. G. B. *Tetrahedron* **1995**, *51*, 11295. Moreover, the classical problem of polyalkylation is circumvented with methyl cyanoformate.
11. a) Hoffmann, H. M. R.; Iqbal, M. N. *Tetrahedron Lett.*, **1975**, 4487 and references therein. b) Reinecke, J.; Hoffmann, H. M. R. *Chem. Eur. J.* **1995**, *1*, 368
12. Overberger, C. G.; Marullo, N. P.; Hiskey, R. G. *J. Am. Chem. Soc.* **1961**, *83*, 1374.
13. *General procedure for the enantioselective deprotonation and methoxycarbonylation of 8-oxabicyclo[3.2.1]oct-6-en-3-one* **1**.[11] A predried 50 mL two-necked flask equipped with a gas inlet and a septum was charged with dry LiCl (25 mg, 0.6 mmol) and heated in a weak stream of nitrogen. THF (20 mL) and (-)-bis[(*S*)-1-phenylethyl]amine[12] (0.28 mL, 1.2 mmol) were added and the stirred solution was cooled to −78 °C. A 1.6 M solution of *n*-butyllithium (0.75 mL, 1.2 mmol) was added dropwise and the solution was allowed to warm to r.t.. After 15 min the mixture was cooled to −94 °C (the colour of the solution turned to violet). Oxabicycle **1** (124 mg, 1.0 mmol) was dissolved in tetrahydrofuran (5 mL) and added dropwise within 15 min. The solution was stirred at −94 °C exactly for 1 h. Then methyl cyanoformate (Mander reagent) (0.55 mL, 5.0 mmol) was added dropwise and the reaction mixture was allowed to warm to r.t. The mixture was worked up by cooling with an ice bath and washing with water (3 × 20 mL). The aqueous phase was reextracted with ether (3 × 20 mL) and the combined organic phase was dried ($MgSO_4$) and concentrated with a rotary evaporator. The resulting red oil (0.52g) was purified by column chromatography (PE/E, 3 : 1 → 1 : 1, 50 g silica gel) to yield 130 mg of (+)-**2** (71%) as a slightly yellow, viscous oil. Spectroscopic data for (+)-**2** were identical with the data of racemic **2**. $[\alpha]_D^{21}$ = +2.1° (c = 1, $CHCl_3$); IR ($CHCl_3$) ν 3040, 2972, 2956, 1740, 1720, 1436, 1408, 1336, 1324, 1300, 1260, 1228, 972, 864, 844 cm^{-1}; ^1H NMR δ 1.61 (br. s,1 H), 2.38 (d, J = 16 Hz, 1 H), 2.78 and 3.01 (2 x dd, J = 16/5 Hz, 1 H), 3.79 (d, J = 4 Hz, 3 H), 3.88 (d, J = 4 Hz, 3 H), 5.08 (m, 1 H), 5.15 (dd, J = 4/2 Hz, 1 H), 5.34 (s, 1H), 6.23-6.43 (m, 2 H), 6.56 (dd, J = 6/2 Hz, 2 H); MS *m/z* 182 (M^+, 11), 164 (21), 151 (23), 140 (25), 124 (20), 108 (24), 101 (61), 95 (12), 82 (100), 69 (66).

Note added in proof: Since the submission of our manuscript a route to the C(18)-C(23) segment of lasonolide A from a protected α-D-glucopyranoside has been outlined (*three* stereogenic centres, ca. 18 steps). See Gurjar, M. K.; Kumar, P.; Rao, B. V. *Tetrahedron Lett.* **1996**, *37*, 8617.

(*Received in Germany* 25 *November* 1996; *accepted* 16 *December* 1996)