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Tetrahedron Letters 44 (2003) 4343–4346

TETRAHEDRON LETTERS

The first stereoselective total synthesis of lankanolide. Part 1: Computer-assisted design and lactonization of model *seco*-acid derivatives

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Received 6 March 2003; revised 7 April 2003; accepted 11 April 2003

Abstract—To design easily cyclizable *seco*-acid derivatives of lankanolide, the conformation of several model *seco*-acids was calculated and the lactonization experiments of the *seco*-acids were carried out to elucidate the efficiency of the cyclization of the model *seco*-acid. © 2003 Published by Elsevier Science Ltd.

The target molecule, lankanolide **2** is the aglicone of 14-membered macrolide lankamycin **1**. Lankamycin was isolated in 1960 by Gaumann et al.,[1] and the relative stereo-structure of the macrolide was determined in 1972 by Keller-Schlierlein et al. (Fig. 1, Scheme 1).[2] Since then, no report of the total synthesis of this macrolide has appeared, while synthetic efforts have been carried out.[3] We are interested in the effect of the structure of the *seco*-acid derivative on the efficiency of macrolactonization. In some cases, *seco*-acid derivatives did not cyclize to give macrolactone derivatives. To avoid such a case, we decided to design the target *seco*-acid derivatives by computer-aided simulation before starting the synthesis.[4] In our design, there are two routes depending on whether before cyclization, C8 is quaternalized (route a) or after cyclization, an asymmetric center at C8 is introduced (route b). Route a is via *seco*-acid **II** which has a tertiary alcohol at the C8 position. In route b, macrolactone **IV** is oxidized to prepare a tertiary alcohol at the C8 after cyclization. The critical point of these two routes will be the reactivity of *seco*-acids **II** and **V**. To predict the reactivity of *seco*-acids **II** and **V**, first, we calculate the conformation of the methyl ester of model *seco*-acid derivatives (**4**, **6** and **8**) corresponding to *seco*-acids **II** and **V**, and the lactones (**3**, **5**, and **7**) (Fig. 2).

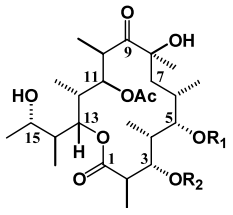

Figure 1. Lankamysin and lankanolide. Lankamysin (**1**): R_1 = D-chalcose, R_2 = acetylarcanose. Lankanolide (**2**): R_1 = H, R_2 = H.

Recently Goto et al. developed a conformational search method of chain compounds by stepwise bond rotation (conflex).[5] First, we generated the three-dimensional structures by using 'conflex' and the obtained conformers were classified to conformation clusters.[6] As shown in Figure 3, the simulated conformation of the methyl ester of the *seco*-acid **4** showed a conformation cluster (15.2%) of the *seco*-acid has a similar conformation to the corresponding cluster of lactone **3** (conformation distance = 8.7).[7,8] On the other hand, the calculated conformation of diacetonide *seco*-acid **6** showed no similar conformation to the corresponding lactone **5** (conformation distance = 48.1).[8] The simulated conformation of **8** methyl ester also did not contain a similar conformation to the corresponding lactone **7** (conformation distance = 49.7).[8] This result suggests that the *seco*-acid **4** having a similar conformation to the corresponding lactone will easily cyclize to form macrolactone.[8] The *seco*-acid having a tertiary alcohol at C8 (**8**) and diacetonide *seco*-acid **6** were predicted not to cyclize easily.

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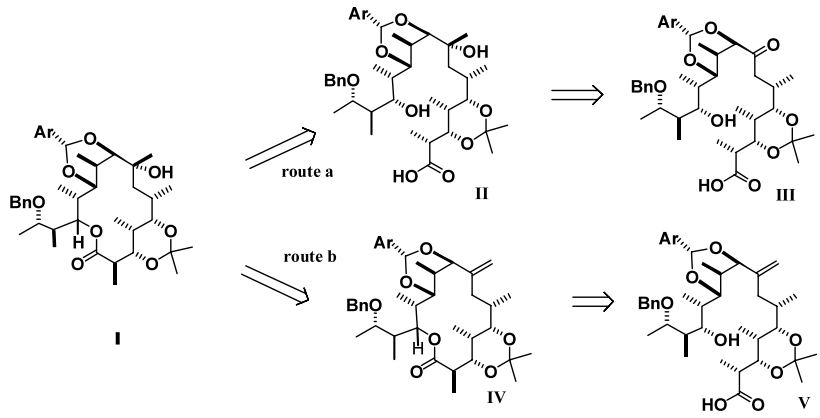
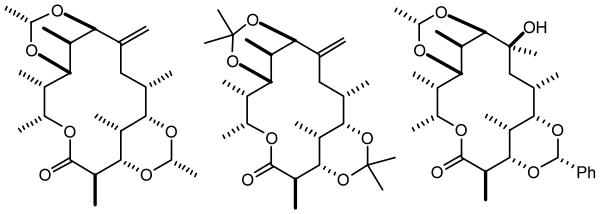
0040-4039/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0040-4039(03)00954-7



Scheme 1. Retro synthetic analysis of lankanolide.



model lactone: **3** seco-acid of **3**: **4**
model lactone: **5** seco-acid of **5**: **6**
model lactone: **7** seco-acid of **7**: **8**

Figure 2. Model *seco*-acids and lactones for conformation calculation.

To test the predicted reactivity of these three types of *seco*-acids, we synthesized several model *seco*-acids, and performed cyclization experiments. The *seco*-acids (**12**, **14** and **18**) were prepared starting from the known intermediate **9** reported by Paterson et al.,[9] as shown in Schemes 2 and 3. The iodide **9** was converted to epoxy-acetonide **10** via deoxygenation to form *exo*-olefin, following 1,2-reduction of enone to give diol **11** as a single diastereomer. The *seco*-acid **12** and **14** were synthesized by a similar method. The diol of **11** was acetalized with mesitaldehyde dimethylacetal and hydolyzed with NaOH to form *seco*-acid **12**. Similar treatment of **11** with 2-methoxypropene, and NaOH gave *seco*-acid **14**. The *seco*-acid **18** was also synthesized starting from **9**, as shown in Scheme 3. Diol of **9** was protected as a mesitilidene acetal, following reduction of ketone, and the resulting diol was again protected as a mesitilidene acetal to give **16**. The lactone and epoxide were reduced with LAH to form a triol, and the primary alcohol of the triol was protected as a

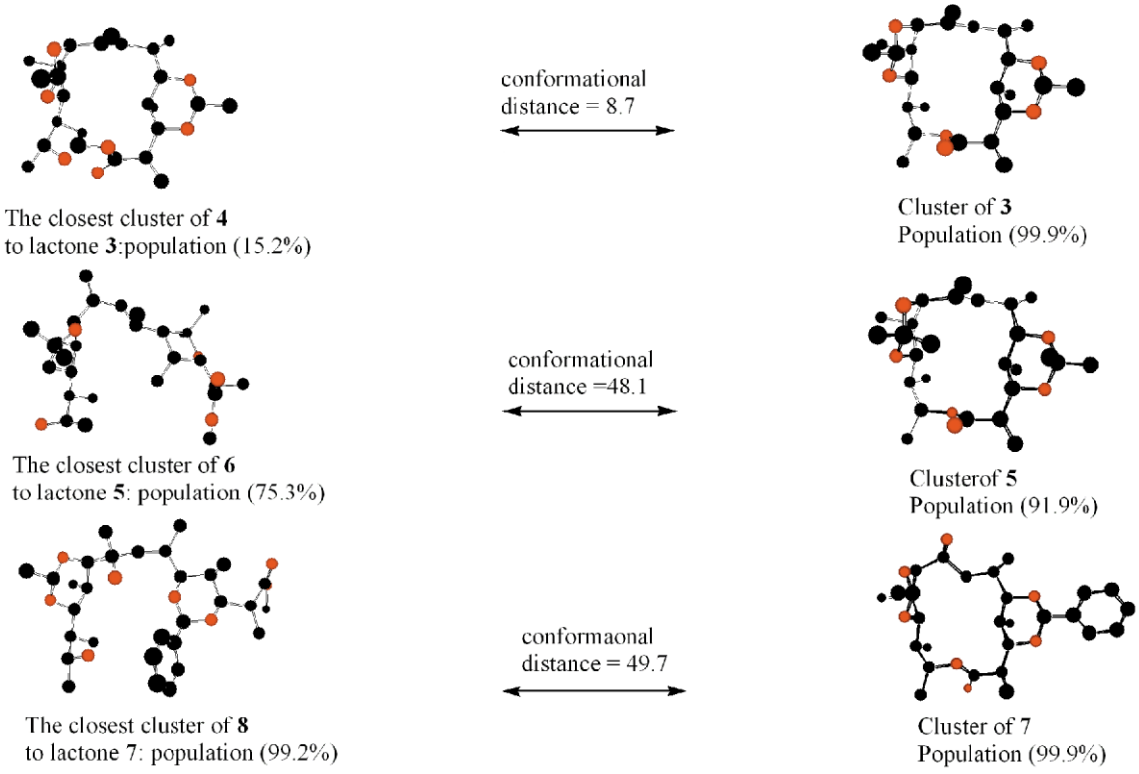
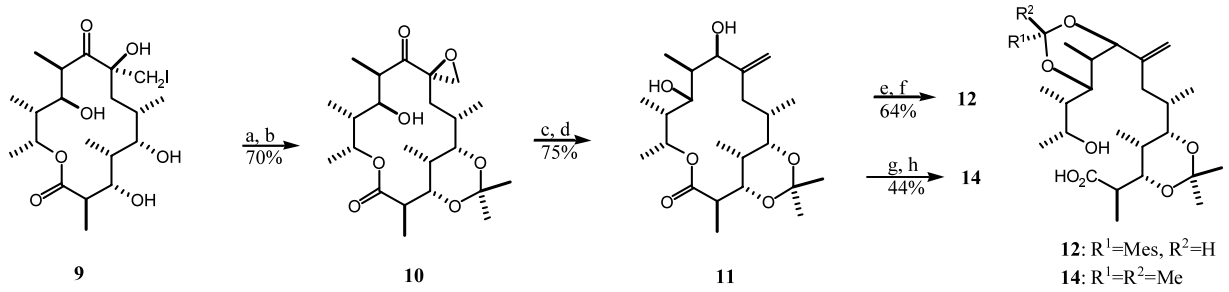
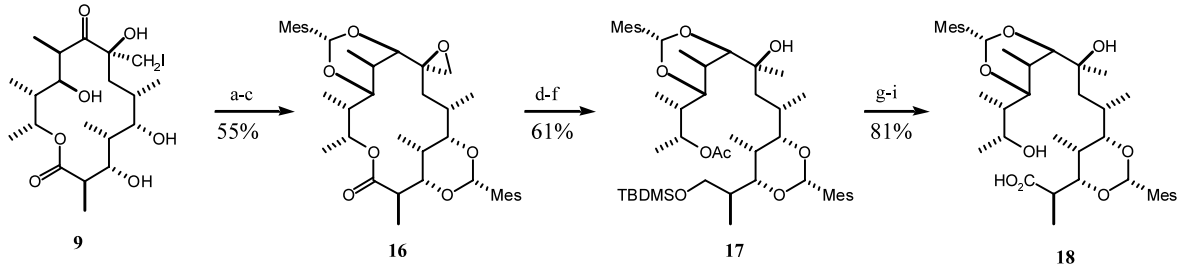


Figure 3. Conformational distance between the cluster of lactone (**3**, **5** and **7**) and the corresponding *seco*-acid (**4**, **6** and **8**).



Scheme 2. Preparation of model *seco*-acid derivatives **12** and **14**. *Reagents and conditions*: (a) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt, 1 h; (b) aq-$NaHCO_3$, THF, rt, 20 min; (c) $CrCl_2$, acetone–H_2O (2:1), rt, 30 min; (d) $NaBH_4$, $CeCl_3$, THF, −25°C, 4.5 h; (e) $MesCH(OMe)_2$, CSA, CH_2Cl_2, rt, 6 h; (f) 5N NaOH, DMSO, 90°C, 12 h; (g) 2-methoxypropene, PPTS, CH_2Cl_2, rt, 45 min; (h) 5N NaOH, DMSO, 90°C, 12 h.



Scheme 3. Preparation of *seco*-acid derivative **18**. *Reagents and conditions*: (a) $MesCH(OMe)_2$, CSA, CH_2Cl_2, rt, 30 min. (b) $NaBH_4$, *i*-PrOH–AcOEt (2:1), rt, 20 min. (c) $MesCH(OMe)_2$, CSA, CH_2Cl_2, rt, 5 h. (d) $LiAlH_4$, Et_2O, 30°C, 2 h. (e) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt, 24 h. (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 33 h. (g) *n*-Bu_4NF, THF, rt, 3.5 h. (h) Jones reagent, acetone, −30°C, 5 h. (i) 15% NaOH, MeOH, rt, 24 h.

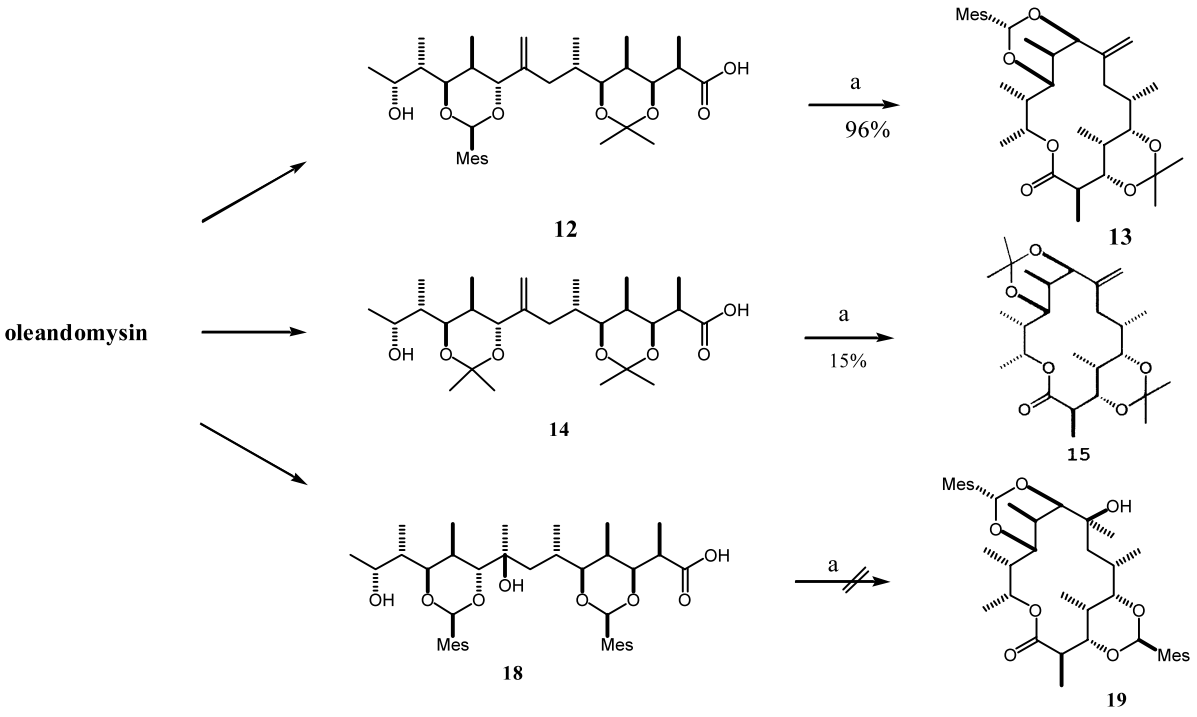
Table 1. Cyclization reactions of several *seco*-acids

seco-Acid (mM)	Cyclization method[a]	DMAP (mol equiv.)	Reaction temp.	Reaction time (h)	Yield (%)
12 (1.0)	A	2.5	130	11	96
12 (1.0)	B	3	Rt	3	81
14 (1.0)	A	2.5	130	43	15
14 (1.0)	B	2.5	Rt	43	0
18 (1.0)	A	2.5	130	43	0

[a] A: high-dilution condition: To a 6 mM toluene solution of DMPA in toluene, was added slowly a 2 mM toluene solution of the mixed anhydride prepared from *seco*-acid and 2,4,6-trichlorobenzoyl chloride. B: normal condition: DMAP was added to a 10mM toluene solution of the mixed anhydride.

TBDMS ether, and the secondary alcohol was acetylated to give **17**. Deprotection of TBDMS and Jones oxidation followed by deacetylation gave *seco*-acid **18**. The *seco*-acids (**12**, **14** and **18**) were subjected to macrolactonization.

The results of cyclization experiments are shown in Table 1 and Scheme 4. As we predicted, *seco*-acid **12** cyclized smoothly to give macrolactone **13** in high yield, even under the normal concentration conditions. On the other hand, *seco*-acid **14** (diacetonide) cyclized sluggishly to form lactone **15** in low yield even under the high dilution condition. The *seco*-acid **18** did not give **19** at all even under the high dilution condition (Table 1 and Scheme 4). The compatibility between computer-simulated reactivity and chemical reactivity is so important that the computer-simulated conformation analysis may predict the reactivity of intramolecular cyclization, and the most preferable model *seco*-acid to synthesize lankanolide is the *seco*-acid **12**. In some cases, computer-assisted conformation analysis can complement synthetic design. We are continuing research along this line, and in the following report, we describe a successful example of total synthesis of lankanolide via the *seco*-acid designed according to the model *seco*-acid **12**.



Scheme 4. Effect of C8 functional groups on macrolactonization. *Reagents and conditions*: (a) To a solution of DMAP was added slowly a dilute solution of the mixed anhydride prepared from *seco*-acid (**12**, **14** and **18**) and 2,4,6-trichlorobenzoyl chloride.

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3. Fragment synthesis: (a) Kotchetkov, N. K.; Yashunsky, D. V.; Sviridov, A. F.; Ermenko, M. S. *Carbohydr. Res.* **1990**, *200*, 209; (b) Raimundo, B. C.; Heathcock, C. H. *Synlett* **1995**, 1213; (c) Paterson, I. *Tetrahedron Lett.* **1983**, *24*, 1311.
4. For a previous report related to conformation analysis for synthetic design; see: Makino, K.; Nakajima, N.; Hashimoto, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 9077 and references cited therein.
5. Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 187. We used the latest version 4.02 of conflex working on pc-unix (linux) and using extended MM2 as a force field.
6. Similar conformation (differences of all dihedral angle to be compared are less than 10 degree) is classified in one cluster. The conformation of the cluster to be compared is more similar each other, the conformation distance is smaller.[7] Obtained number of conformers having more than 0.01% population are shown below: 120 for **4**, 256 for **6**, 153 for **8**, 2 for **3**, 4 for **5**, 11 for **7**.
7. (a) Osawa, E.; Goto, H.; Hata, T.; Deretey, E. *J. Mol. Struct. (Theochem.)* **1997**, *398–399*, 229; (b) for the definition of cluster distance, see: Saunders, M. *J. Comput. Chem.* **1991**, *12*, 645.
8. It is well known that the six-membered ketal of *anti*-1,3-diol prefer twist-boat type,[10] and the most preferable conformer of six-membered ketal of *anti*-1,3-diol (C9, C11) of model *seco*-acid **6** was also twist-boat (Fig. 3). However, the most of the conformation of the corresponding lactone **5** was chair type (Fig. 3). Therefore, twist-boat conformer has to change to the more unstable chair conformer before cyclization.
   Most of the conformation of model compound **8** is locked as shown in Figure 3, mainly because of hydrogen bonding between tertiary alcohol at C8 and ether oxygen of six-membered ketal of C3 and C5 diol. Because of the locked structure, the reaction point (alcohol at C13 and terminal carboxylic acid) can not approach each other. Both conformations of the six-membered acetal and ketal of *syn*-1,3-diol (C3,C5) of *seco*-acids **4**, **6** and **8** were shown to be fixed to chair conformation.[10] The substituents (methyl or phenyl or dimethyl group) on the six-membered ring of the *syn*-1,3-diol are far from backbone chain, we can conclude that the difference of the substituents do not affect the backbone conformation.
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