Pergamon

Tetrahedron Letters 40 (1999) 1375–1378

TETRAHEDRON
LETTERS

New synthetic methodology to prepare polyfunctionalized heptane building blocks with four stereocenters: synthesis of the (±)-C17-C23 subunit of Ionomycin

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Received 13 October 1998; accepted 8 December 1998

Abstract:

A new synthetic methodology for preparing polyfunctionalized heptane building blocks with up to four stereocenters has been developed. 2,4-Dimethyl-1-methoxy-8-oxabicyclo-[3.2.1]-oct-6-en-3-one has been used as precursor, which can be easily prepared by a [4+3] cycloaddition reaction between 2-methoxy-furan and the oxyallyl cation generated *in situ* from 2,4-dibromo-3-pentanone. The cycloadducts have an acetal functionality on C1 which allows easy opening of the oxabicyclic system, affording versatile synthons. The application of this methodology to the synthesis of the C17-C23 subunit of Ionomycin is presented.

Keywords: Cycloadditions, cycloheptenes, antibiotics, bridgehead chemistry.

The C1-functionalized 2,4-dimethyl-8-oxabicyclo-[3.2.1.]-oct-6-en-3-ones, whose synthesis and applicability have been studied by us, [1,2,3,4], are readily available by [4+3] cycloaddition reactions between C2-functionalized furans and the oxyallyl cation derived from 2,4-dibromo-3-pentanone (Fig. 1). The cycloadducts have at C1 an acetal function which allows an easy oxygen-bridge opening or a further chemical derivatization.

Discrimination between the ketone group at C3 and the masked carbonyl group on C1 has been accomplished by a highly stereoselective reduction of the C3-carbonyl group to the corresponding alcohol. Further hydrolysis of the cyclic acetal affords a versatile building block which could be readily transformed into linear seven-membered synthons with four different organic functional groups and up to four stereocenters.

Application of this methodology to the synthesis of the C17-C23 fragment of antibiotic Ionomycin is also described (Fig 1).

PII: S0040-4039(98)02612-4

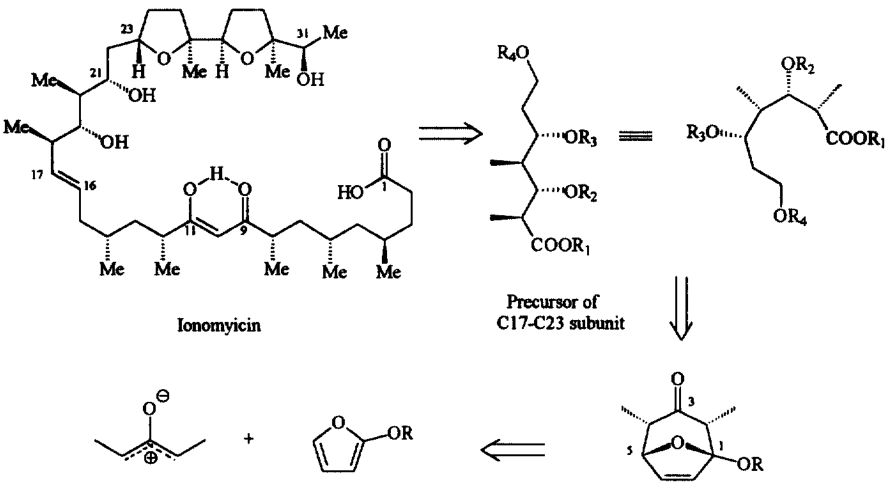


Figure 1.- Retrosynthetic approach to the C17-C23 subunit of antibiotic Ionomycin.

The C17-C23 subunit of the macrolide antibiotic Ionomycin is an important synthetic target and its synthesis has been carried out in the past by other methodologies [5,6]. A new approach, starting from cheap and commercially available precursors, and involving versatile intermediates is presented here, (Fig. 2).

The [4+3] cycloaddition reaction between 2-methoxyfuran and the oxyallyl cation, generated *in situ* from 2,4-dibromo-3-pentanone by the reducing system Cu/NaI, [7], afforded a mixture of diasteroisomers **1a**/**1b** (Fig. 2) in a 70:30 ratio, with a 97% yield. Both diasteroisomers were easily separated by column chromatography, and both of them were useful for preparing the target molecule. Parallel synthetic pathways have been conducted with both diasteroisomers.

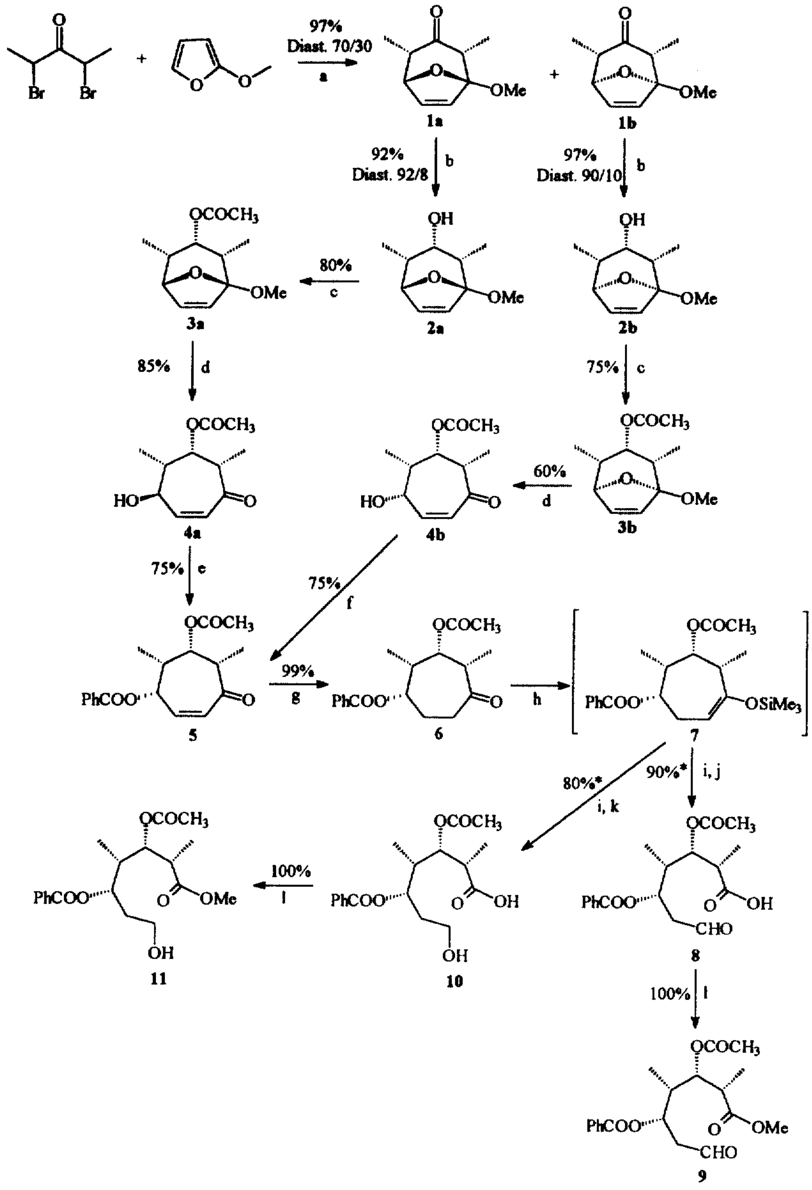
As mentioned before, in order to discriminate the ketone group on C3 (of **1a**) and the masked carbonyl group on C-1 (acetal), reduction of the first one was carried out by using $NaBH_4$ in MeOH with high yield (92%) and diastereoselectivity (92:8) (Figure 1),. The major diastereoisomer of alcohol **2a** was easily purified by column chromatography, of the corresponding acetate **3a**, which was prepared in a 80% yield by treatment of **2a** with 1 equivalent of MeLi at 0°C, followed by CH_3COCl.

In this synthetic pathway, cleavage of the oxygen bridge by hydrolysis of the acetal group on C1 was a key step. This hydrolytic opening was carried out under controlled conditions by using 1 equivalent of CF_3COOH and 10 equivalents of H_2O in $CHCl_3$, at room temperature, affording the compound **4a** in a 85% yield.

In order to get the right configuration on the carbon bearing the hydroxyl group in **4a** (C21 in Ionomycin), it was necessary to carry out an inversion of configuration at that center (C4) by the Mitsunobu reaction, [8,9], which resulted in simultaneous protection, as a benzoate (**5**), of the inverted hydroxyl group.

Compound **5** was obtained in a parallel way starting from cycloadduct **1b**, following a synthetic pathway similar to that described before for **1a**. In this case, the Mitsunobu reaction

was not necessary because the intermediate 4b had the right configuration at all four stereocenters.



a) Cu, NaI, CH_3CN, (chromatographic separation); b) $NaBH_4$, MeOH, (chromatographic separation); c) 1) MeLi, 0°C, THF, 2) CH_3COCl, THF; d) CF_3COOH, H_2O, $CHCl_3$; e) PhCOOH, DEAD, Ph_3P, THF; f) Et_3N, DMAP, PhCOCl, $CHCl_3$; g) H_2, Pd(10%)/C, THF; h) LDA, Me_3SiCl, HMPA -78°C, THF; i) O_3, CH_2Cl_2/MeOH 1/1, -78°C; j) Me_2S, CH_2Cl_2/MeOH 1/1; k) $NaBH_4$, CH_2Cl_2/MeOH 1/1; l) CH_2N_2, Et_2O. (*) Overall yield of steps: h,i,j or h,i,k

Figure 2.- Synthetic pathway to obtain the building blocks 8(9) or 10(11), precursors of the (±)C17-C23 subunit of Ionomycin.

Catalytic hydrogenation of **5** gave in almost quantitative yield compound **6**. Reaction conditions were optimized in order to avoid hydrogenolysis of the benzoate group which is in an allylic position, [10,11,12]. Cleavage of the cycloheptane ring was performed *via* formation of silyl enol ether **7**, followed by ozonolysis. Intermediate **7** was not isolated but treated, in one pot, with O_3. This approach afforded better results than isolating the silyl enol ether **7**, due to its unstability.

Ozonolysis was conducted with two different reductive cleavage conditions. First, Me_2S was used [13] as a reducing agent for the intermediate ozonide, affording the 6-formyl hexanoic acid **8** in 90% overall yield, (steps h, i, j). When reduction of ozonide was performed by using $NaBH_4$ in CH_2Cl_2/MeOH [13,14,15,16] the 7-hydroxy-heptanoic acid **10** was obtained. Both acids, **8** and **10**, were protected as their methyl esters, **9** and **10**, respectively, with CH_2N_2 in quantitative yield.

Using our new synthetic methodology we have prepared, in seven steps, with high yield and diastereoselectivity, the building blocks **8** and **10**, (eight steps for **9** and **11**), which have four different functional groups and four stereocenters. The presence of two well-differentiated functionalities on each end of the carbon chains of **8/10** or **9/11** allows their sequential connection to other building blocks.

The extension of this synthetic methodology to other target molecules is under study in our laboratory. All the compounds mentioned in this paper have been conveniently purified by column chromatography and properly characterized by spectroscopic methods and elemental analysis.

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