Pergamon

Tetrahedron Letters, Vol. 35, No. 24, pp. 4197-4200, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0744-I

Synthesis of (+)-Gabosines C and E from D-Ribose.

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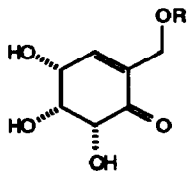
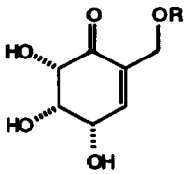
Abstract: *Short syntheses of Gabosines C (1) and E (3), starting from D-ribose are reported. The syntheses employ an intramolecular nitrile oxide cycloaddition to generate the carba-sugar skeleton, and result in the first total syntheses of unnatural (+)-Gabosine C and natural (+)-Gabosine E.*

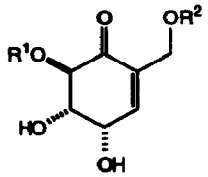
The gabosines are a family of unusual carba-sugars that have recently been isolated from Streptomyces[1], with perhaps the most interesting representatives being Gabosines C (1) and E (3). Natural gabosine C (-)-(1) is identical to the known antibiotic KD16-U1[2] and gabosine E has been reported to have weak but somewhat intriguing activity as an inhibitor in the biosynthesis of cholesterol[1]. In addition, ester derivatives of both of these natural products have been isolated. The crotonyl ester of gabosine C, known as COTC (-)-(2) has been known for a number of years, and has been shown to be a potent glyoxylase inhibitor[3], and recently the acetyl derivative of gabosine E, known as gabosine D (4a) and the 2-hydroxy-3-methylbenzoate derivative (4b) have also been isolated[1,4]. As a consequence of the interesting biological activity of COTC (-)-(2), there have been a number of syntheses of this molecule reported[5], however as far as we are aware the gabosine E (3) system has not previously been prepared. As part of a research programme to develop novel enzyme inhibitors we were interested in developing synthetic approaches to these systems. Since it is known that the biological activity of COTC requires the enone moiety to be intact[6], we were interested in obtaining the unknown antipode (+)-(2), in order to assess the effect of this change on its biological activity, and we now report the first syntheses of both (+)-(1) and (+)-(3) from D-ribose.



(-)-(1), R = H
(-)-(2), R = crotonyl



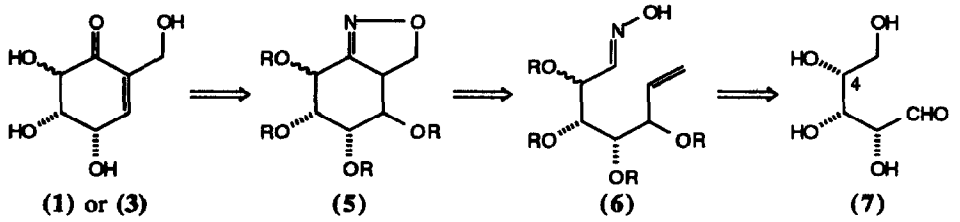
(+)-(1), R = H
(+)-(2), R = crotonyl



(+)-(3), $R^1 = R^2 = H$
(+)-(4a), $R^1 = H$, $R^2 = Ac$
(+)-(4b), R^1 = 2-hydroxy-3-methyl benzoate, $R^2 = H$

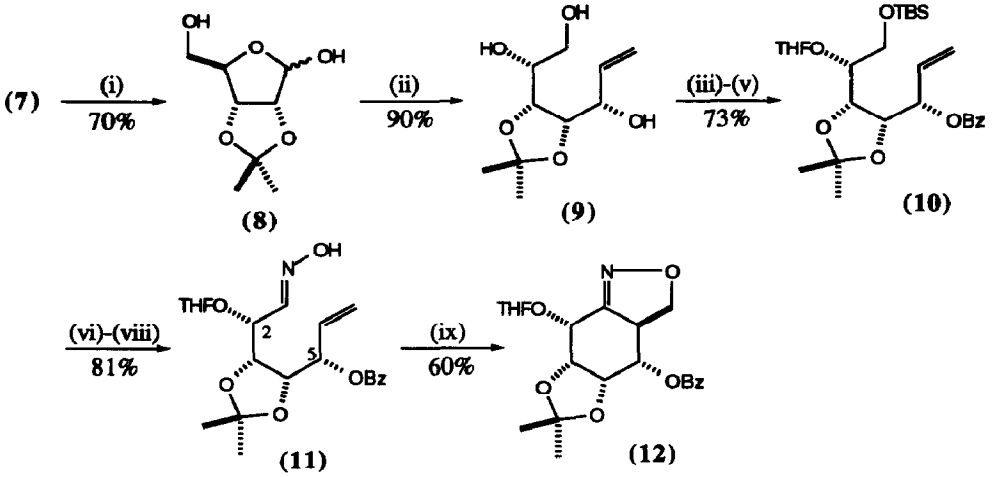
Since both gabosines C (1) and E (3) contain an enone system with an hydroxymethyl substituent in the 2-position, it would seem that these molecules are ideally suited to synthesis *via* an intramolecular nitrile oxide

cycloaddition (INOC) approach[7] (scheme 1), this should allow such a system to be rapidly set up from cycloadducts of type (5). We considered that the precursors to the cycloadduct should be readily accessible from natural sugars, and that it may be possible to prepare both isomers from D-ribose (7), if epimerization at C-4 could be achieved at some stage during the synthesis.



Scheme 1

To this end we examined the preparation of the cycloadduct (5) and this is outlined in scheme 2. Reaction of D-ribose with 2,2-dimethoxypropane gave the mono-acetonide (8), which was then treated with an excess of vinylmagnesium bromide to give alkene (9). Although irrelevant in the context of the overall target, the Grignard addition was shown to proceed with good selectivity, and this is consistent with observations on related reactions of ribose derivatives[8]. Compound (9) has the compete carbon backbone required, and so conversion to the cycloaddition precursor simply required oxidation of the primary hydroxy group, and conversion to the corresponding oxime. At this stage it was unclear whether it would be necessary to have the remaining secondary hydroxyls protected for the cycloaddition or not, however since selective oxidation attempts were unsuccessful we elected to take the safe strategy of alcohol differentiation *via* selective protection.



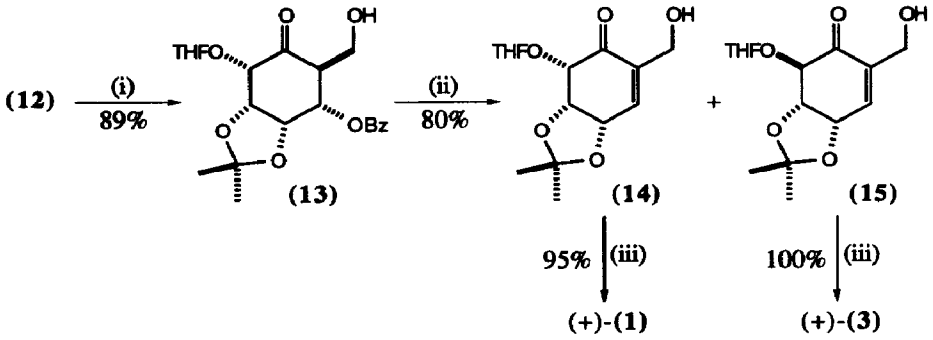
Scheme 2

Reagents: (i) 2,2-dimethoxypropane, acetone, CSA; (ii) vinylmagnesium bromide (10eq), THF, rt; (iii) TBS-Cl, pyridine, DMAP; (iv) Bz-Cl, pyridine; (v) 2,3-dihydrofuran, PPTS, CH_2Cl_2; (vi) Bu_4NF, THF, rt; (vii) $(COCl)_2$, DMSO, Et_3N, THF; (viii) $HCl.H_2NOH$, pyridine, MeOH, rt; (ix) NaOCl, Et_3N, CH_2Cl_2.

Fortunately this could readily be achieved, the primary hydroxyl as might be expected was the most reactive, and once this had been blocked with a tert-butyldimethylsilyl group (TBS), the more reactive allylic hydroxyl could also be differentiated. This allowed investigation of a range of protecting group combinations

and their consequences on subsequent transformations, and ultimately led to the identification of the benzoate (Bz), tetrahydrofuranyl (THF) derivative (**10**) as the most useful intermediate. This material could readily be converted into the required oxime (**11**) using standard procedures.

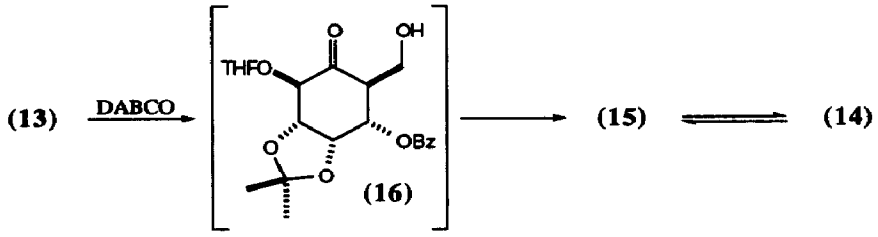
With the cyclisation precursor in hand, we next examined the INOC reaction and found that it could be readily achieved using sodium hypochlorite, giving the cycloadduct (**12**) in good yield and with good stereoselectivity. Our studies on the cycloaddition reaction with other protecting group combinations clearly demonstrated that ester derivatives (acetate or benzoate) of the C-5 hydroxyl group were essential for efficient cycloaddition. With other protecting groups the cycloaddition yields dropped dramatically (0-30%), and it is interesting to note that other reports of the INOC reaction involving carbohydrate derivatives[9] seem to indicate that the correct choice of protecting groups is crucial to successful reaction.



Scheme 3

Reagents: (i) H_2, Ni(R), EtOH, AcOH; (ii) DABCO, THF; (iii) TFA, CH_2Cl_2.

Conversion of the cycloadduct (**12**) into (+)-gabosines C (**1**) and E (**3**) is outlined in scheme 3, and initially involved reductive cleavage of the isoxazole ring to give the ketone (**13**). At this stage we required to effect elimination of benzoic acid in order to obtain the required enone functionality. Clearly this is a not a straightforward operation since the enone product (**14**) is very susceptible to aromatisation under basic conditions. After extensive investigation we found that the desired elimination could be effected in good yield using DABCO in dry THF, however under these conditions epimerisation of the tetrahydrofuranyloxy-substituent also occurred.



Scheme 4

Detailed study of this reaction revealed that the epimerisation reaction was occurring rapidly prior to elimination, to give exclusively the C-6 epimer (**16**) which is clearly favoured in that the tetrahydrofuranyloxy-group is now in the more stable equatorial arrangement (scheme 4). This intermediate then underwent elimination of benzoic acid to give enone (**15**), possessing the correct stereochemistry for (+)-gabosine E (**3**). After elimination a slower epimerisation reaction led to the formation of enone (**14**),

possessing the correct stereochemistry for (+)-gabosine C (1), and at equilibrium the mixture of enones (15):(14) was 2:1. Consequently enone (15) could be isolated in good yield if the reaction was allowed to proceed for 24h, and enone (14) could be generated if longer reaction times were used.

The conversion of enones (14) and (15) into (+)-gabosines C (1) and E (3) was simply achieved by treatment with trifluoroacetic acid. The spectroscopic data for (+)-gabosine C (1) prepared by this method was in accord with that previously reported in the literature[1] for the natural antipode, but as expected it's specific rotation was oposite in sign. Synthetic (+)-gabosine E (3) exibited both spectral and optical properties consitent with those previously reported for the natural product[1], and consequently we can confirm the structure assigned.

The synthetic route outlined above enables general access to sugar-derived enone systems bearing the hydroxymethyl group at C-2, and so should allow the synthesis of a variety of related systems for biological evaluation.

Acknowledgement: We would like to thank SB Pharmaceuticals and the SERC for a CASE studentship (to M.S.) and the SERC for additional funding. Thanks also to Dr. M. Stuckey for high-field NMR spectra and Mrs. R. Howard for mass spectra.

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(*Received in UK* 24 *January* 1994; *revised* 12 *April* 1994; *accepted* 15 *April* 1994)