following manner: **18***A* was first converted into the 3,11-dibenzoate **19**, which on treatment with sodium methoxide gave the conjugated methyl ester **20**.[3] Reduction of **20** with LAH, followed successively by acetylation and ozonolysis, gave spiro acetatealdehyde **21**. Hydrogenolysis of the benzyl ether group of **21** followed by oxidation gave spirolactone **22**. The spiro acetate-aldehyde **21** was also reacted with the zirconium enolate of methyl propionate (6, 7) to yield the adduct **23***A* and its C-2 epimer **23***B* (not shown), in a 10:1 ratio, which were separated by chromatography. Treatment of **23***A* with potassium carbonate in methanol gave spiro compound **18***A*.

Acknowledgements

This work was financially supported by the Natural Sciences and Engineering Research Council of Canada (NSERCC) and by the "Gouvernement du Québec: Science et Technologie" (FCAR). An unrestricted grant from Merck Frosst Canada Inc. was also used to support this work.

[3] A small quantity of the C-2 epimer **18***B* (not shown) of **18***A* was also isolated from this reaction.

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Formal total synthesis of erythromycin A. Part III. Synthesis of Woodward's carbamate key intermediate from a 1,7-dioxaspiro[5.5]undecane derivative of erythronolide A

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Received June 24, 1985

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The spirocompound **1** which was obtained by total synthesis (Part I) and by degradation from erythromycin (Part II) was converted into carbamate product **15**, a key intermediate in the Woodward's total synthesis of erythromycin A.

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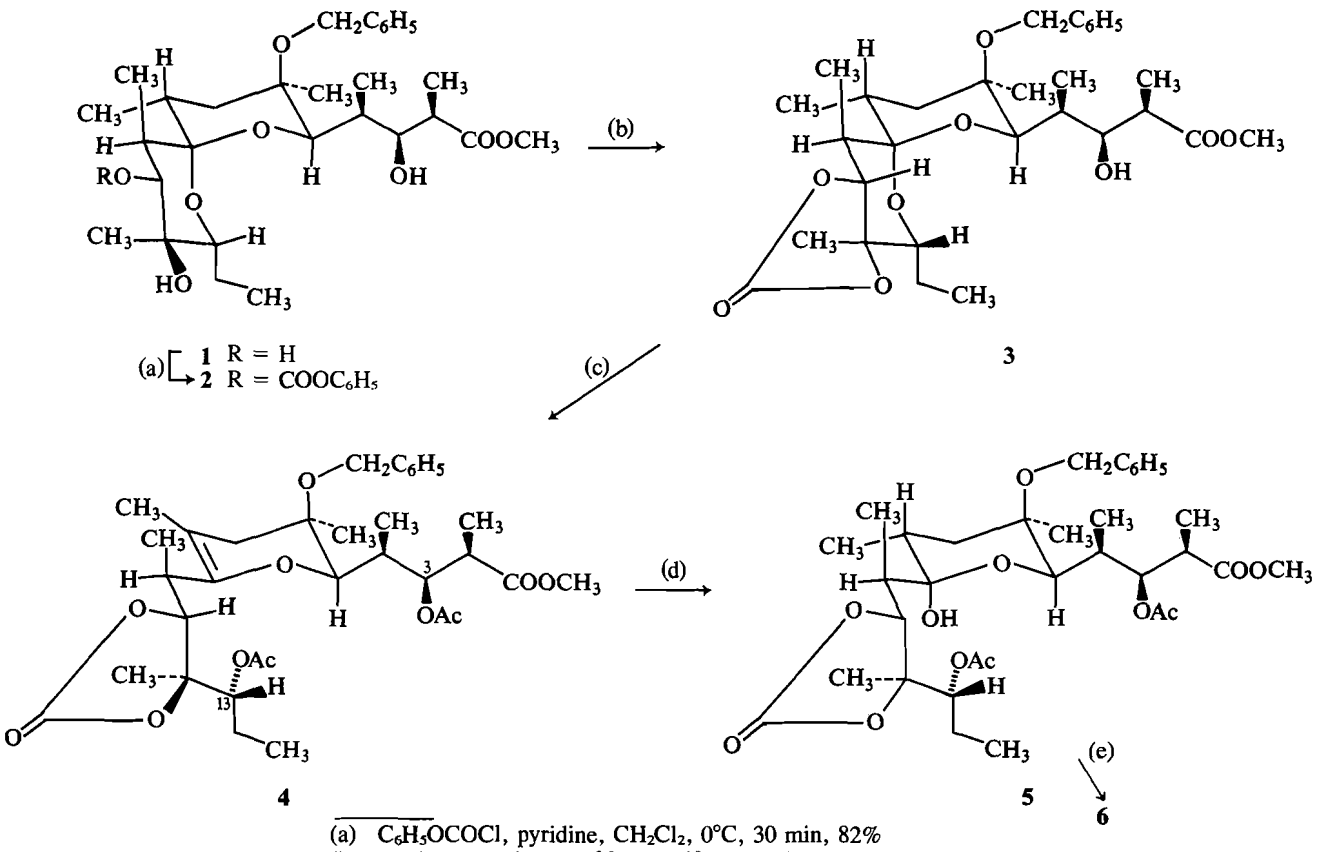
Le composé spiro **1** obtenu par synthèse totale (Partie I) et par dégradation de l'érythromycine A (Partie II) a été transformé en carbamate **15**, un intermédiaire clé de la synthèse totale de l'érythromycine A rapportée par Woodward et ses collaborateurs.

This communication describes the conversion of the dioxaspiro[5.5]undecane derivative **1** (Scheme 1) into the carbamate derivative **15** (Scheme 2) of the seco acid methyl ester of erythronolide A. Carbamate **15** is one of the key intermediates in the course of the total synthesis of erythromycin A carried out by Woodward et al. (1).

Optically active dioxaspiro[5.5]undecane derivative **1** was prepared by total synthesis and by degradation of erythromycin A (cf. preceding communications, Part I and Part II). Compound **1** was converted selectively into the 11-phenoxy-



(a) C_6H_5OCOCl, pyridine, CH_2Cl_2, 0°C, 30 min, 82%
(b) Imidazole, xylene, 95°C → 100°C, 40 min, 98%
(c) PTSOH, CH_3COOH, $(CH_3CO)_2O$, 60°C → 70°C, 30 min, 81%
(d) HCl (30%), acetone, 25°C, 24 h, 68%
(e) $(CH_3CO)_2O$, $(C_2H_5)_3N$, DMAP, CH_2Cl_2, 25°C, 20 h, 74%

SCHEME 1

carbonate **2**, which was then transformed into the five-membered carbonate derivative **3**.[1]

On treatment of intermediate **3** with *p*-toluenesulfonic acid in a mixture of acetic acid and acetic anhydride, spiroketal ring opening and acetylation took place to yield the substituted dihydropyran 3,13-diacetate **4**.[1] On treatment with 30% hydrochloric acid in acetone, hydration of the tetrasubstituted enol ether in **4** occurred to produce the hemi-ketal **5**.[2,3] Opening of the second ring of the spiroketal was readily achieved by treating hemi-ketal **5** under acetylating conditions, which gave the 6-benzyl 11,12-carbonate 3,5,13-triacetate derivative **6** (Scheme 2) of erythronolide A seco acid methyl ester.

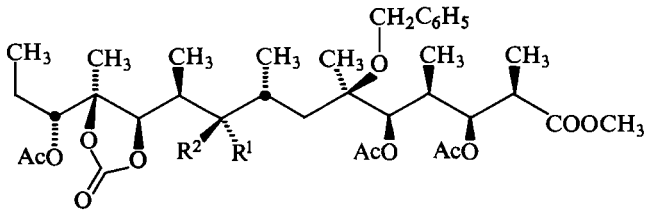
Reduction with sodium borohydride of the ketone function in **6** gave a mixture of 9*R* alcohol **7***A* and the epimeric 9*S* alcohol **7***B* (not shown), in a 2:1 ratio, which were separated by chromatography. The 9*R* alcohol **7***A* was then converted into the 9*S* secondary amine **10** via the intermediate formation of the mesylate **8** and the azide **9** (3). On heating compound **10** in benzene, transacylation between the secondary amino group and the carbonate took place to produce the 6-benzyl 3,5,13-triacetate carbamate derivative **11**.

The next task consisted in removing the benzyl group at C-6 and the triacetate groups at C-3, C-5, and C-13 in order to obtain the Woodward's carbamate intermediate **15**. This could not be achieved directly in two steps and it was found that the methyl ester has to be removed prior to the hydrolysis of the acetate groups. Treatment of compound **11** with lithium iodide in pyridine (4) gave the carboxylic acid **12**, which produced, on basic hydrolysis with sodium hydroxide, the corresponding tetraol carboxylic acid **13**. Esterification of **13** with diazomethane gave the methyl ester **14** which, upon hydrogenolysis with palladium/charcoal, yielded the 9,11-carbamate deriva-

[1] This compound was also prepared by a different route from erythromycin A (cf. Part II).

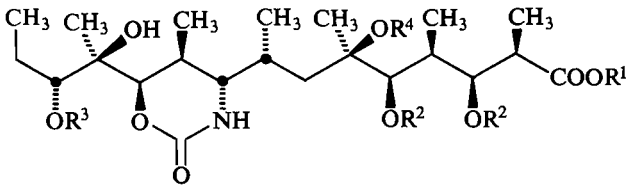
[2] Compound **5** was produced with totally synthetic material as well as with material obtained by degradation of erythromycin A. The remaining work (**5** → **16**) was carried out with material derived from the degradation of erythromycin A.

[3] Stereochemical assignment at C-8 and C-9 was made on the basis that the most stable isomer is expected to be produced under those conditions and by taking into account the principle of stereoelectronic control (2).



(a) **6** R^1, R^2 = O
7A R^1 = H, R^2 = OH
(b) **8** R^1 = H, R^2 = CH_3SO_2
(c) **9** R^1 = N_3, R^2 = H
(d) **10** R^1 = NH_2, R^2 = H

(e)



(f) **11** R^1 = CH_3, R^2 = R^3 = Ac, R^4 = $C_6H_5CH_2$
(g) **12** R^1 = H, R^2 = R^3 = Ac, R^4 = $C_6H_5CH_2$
(h) **13** R^1 = R^2 = R^3 = H, R^4 = $C_6H_5CH_2$
(i) **14** R^1 = CH_3, R^2 = R^3 = H, R^4 = $C_6H_5CH_2$
(j) **15** R^1 = CH_3, R^2 = R^3 = R^4 = H
(k) **16** R^1 = CH_3, R^2 = 2,4,6-trimethylbenzaldehyde acetal, R^3 = R^4 = H

(a) $NaBH_4$, THF, CH_3OH, 25°C, 90 min, 72% yield of *7A* and *7B* (ratio 66:34)
(b) CH_3SO_2Cl, pyridine, 0°C, 20 h, 100%
(c) LiN_3, HMPA, 60°C, 1 h, 91%, ref. 3
(d) PtO_2, H_2, THF, 25°C, 3h, 100%
(e) Benzene, reflux, 120 h, 76%
(f) LiI, pyridine, reflux, 122 h, ref. 4
(g) NaOH 1 *N*, CH_3OH, 25°C, 70 h
(h) CH_2N_2, $CHCl_3$–ether, 25°C, 10 min, 60% yield from **11**
(i) Pd/C (10%), H_2, $CH_3COOC_2H_5$, 25°C, 11 h, 30 min, 85%
(j) Dimethyl acetal of mesitaldehyde, CF_3COOH (cat.), CH_2Cl_2, 0°C, 116 h, 40%, ref. 1

SCHEME 2

tive **15**. Compound **15** was found to be identical[4] with an authentic sample[5] (1) of the 9,11-carbamate derivative of 9*S*-amino-erythronolide A seco acid methyl ester. Acetalization of **15** with mesitaldehyde dimethyl acetal gave the corresponding benzylidene **16**, which was also found to be identical with an authentic sample (1).

Acknowledgements

This work was financially supported by the Natural Sciences and Engineering Research Council of Canada (NSERCC) and by the "Gouvernement du Québec: Science et Technologie" (FCAR). An unrestricted grant from Merck Frosst Canada Inc. was also used to support this work.

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[4] Melting point 164–165°C, mixture mp 164.5–165.5°C, identical ir, 250-MHz ^1H nmr, and tlc.

[5] This sample was kindly provided by the late Dr. K. Sakan.