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Formal total synthesis of erythromycin A. Part II. Preparation of a 1,7-dioxaspiro[5.5]undecane derivative of erythronolide A seco acid methyl ester from erythromycin A

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Degradation of erythromycin A gives spirocompound **18***A*. Compound **18***A* is then converted into the spirolactone **22** via **21**. Compound **21** is then reconverted into spiro product **18***A*.

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Par dégradation, l'érythromycine A fournit le composé spiro **18***A*. Ce dernier est ensuite transformé en spirolactone **22** via **21**. Le composé **21** est ensuite reconverti en produit spiro **18***A*.

This communication describes the transformation of erythromycin A (**1**) (Scheme 1) into the 1,7-dioxaspiro[5.5]undecane derivative **18***A* (Scheme 3) of the seco acid methyl ester of erythronolide A. The degradation of the side chain of triol ester **18***A* to give spirolactone **22** via the spiroaldehyde **21** is also reported, as well as the reconstruction of triol ester **18***A* from spiroaldehyde **21**.

Erythromycin A (**1**) was first converted into dihydroerythronolide A (**2**) (1) using the four-step sequence developed by Jones and Rowley (2). In the next operation, the four secondary alcohols were protected by converting **2** into the bis-acetonide **3**, and the remaining two tertiary alcohols were then protected by benzylation (**3** → **4**). Acid hydrolysis of **4** removed both acetonide protecting groups yielding the bis-benzyl ether tetraol **5**, which was then selectively converted into the monoacetonide bis-benzyl ether 9,11-diol **6** using pyridinium tosylate (3) and 2-methoxypropene.

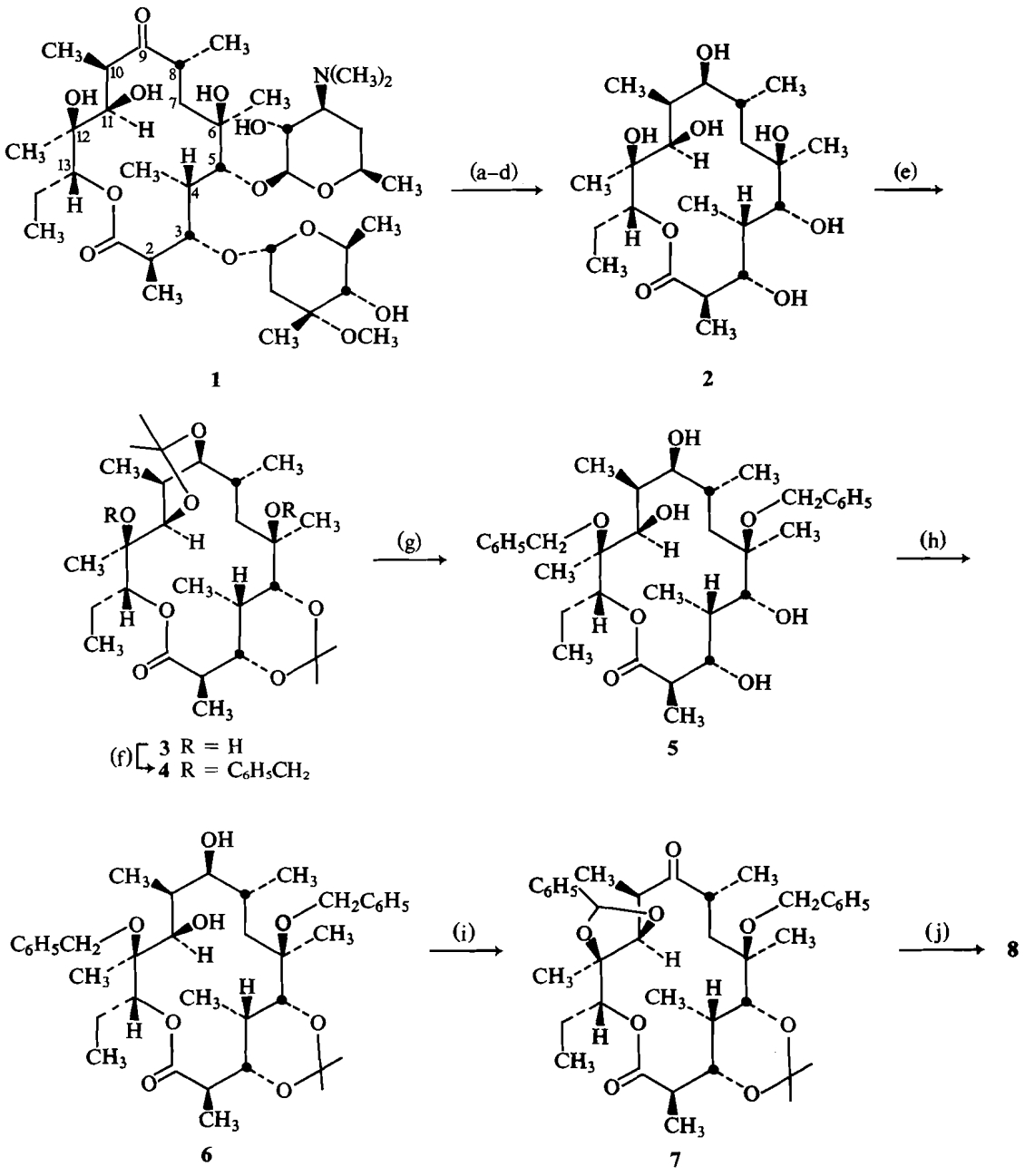
In the next step, pyridinium chlorochromate oxidation of **6** gave the benzylideneacetonide ketone **7**. In this reaction, in addition to the oxidation of the secondary alcohol at C-9 (4), and unexpectedly, the benzyl ether at C-12 was selectively oxidized and transformed into a C(11)—C(12) benzylidene protecting group.

Treatment of **7** with aqueous acetic acid gave 6-benzyl ether-11,12-benzylidene derivative **8** of 8-epi-erythronolide A (Scheme 2). In this reaction, the acetonide group was selectively hydrolyzed with concomitant epimerization of the C-8 methyl group.[1] The seco acid methyl ester derivative **9** of 8-epi-erythronolide was then obtained from **8** using sodium methoxide in methanol. Treatment of **9** with aqueous acetic acid gave the dioxaspiro[5.5]undecane derivative **10**.[2]

The 8-epi-spiro derivative **10** was first converted into the

[1] The epimerization at C-8 has precedent in the literature (5). It was established by the fact that **8** gives the 8-epi-spiro **10** which, when converted into 8-epi-spirocarbonate **12**, undergoes equilibration to give the more stable spirocarbonate **17** (*vide infra*).

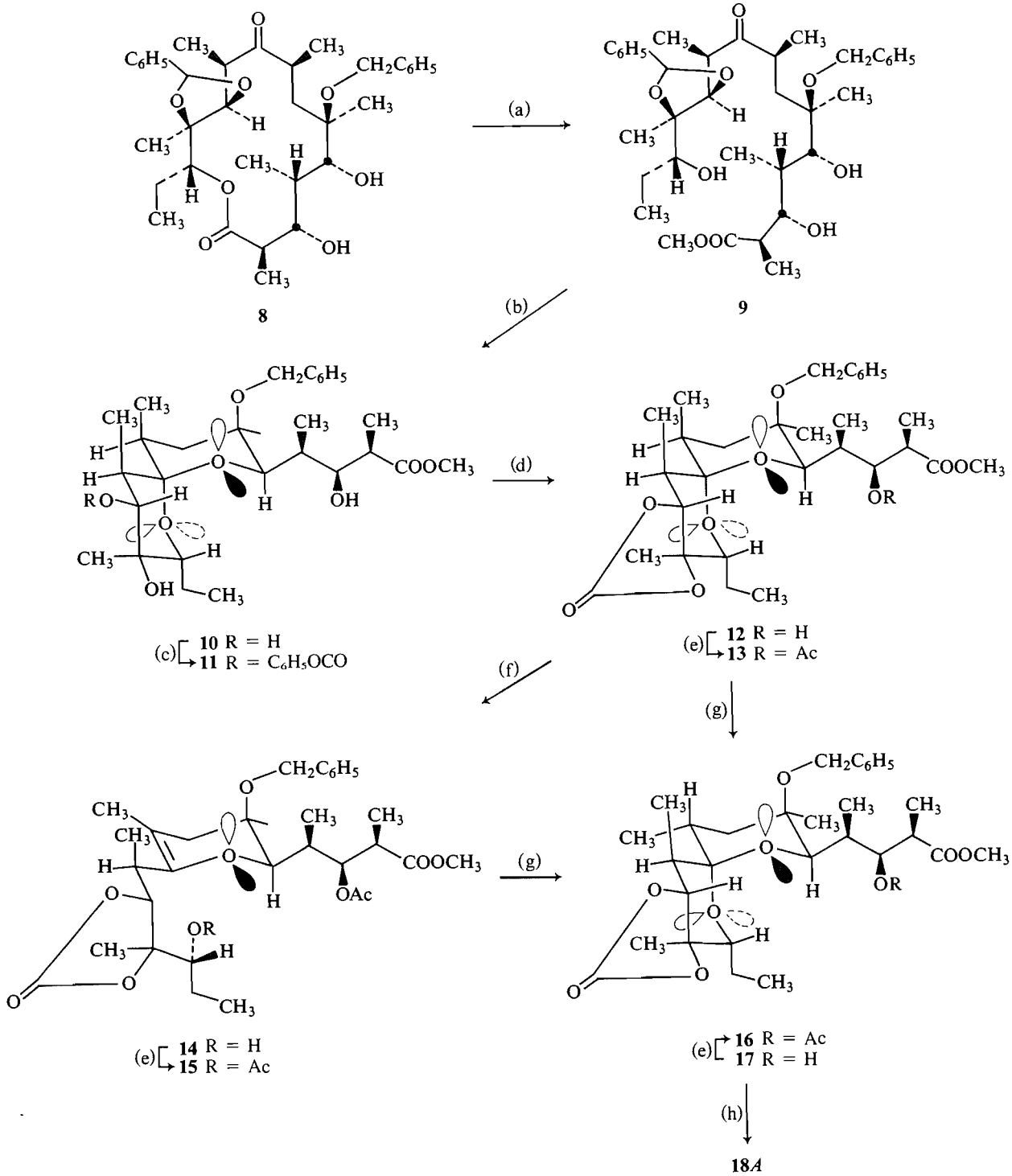
[2] In the sequence **9** → **10**, spiroacetalization took place prior to the hydrolysis of the benzylidene protecting group because the C(11)—C(12) benzylidine derivative of **10** can be isolated as an intermediate product when the reaction is stopped before completion.



1 2 5 6 7

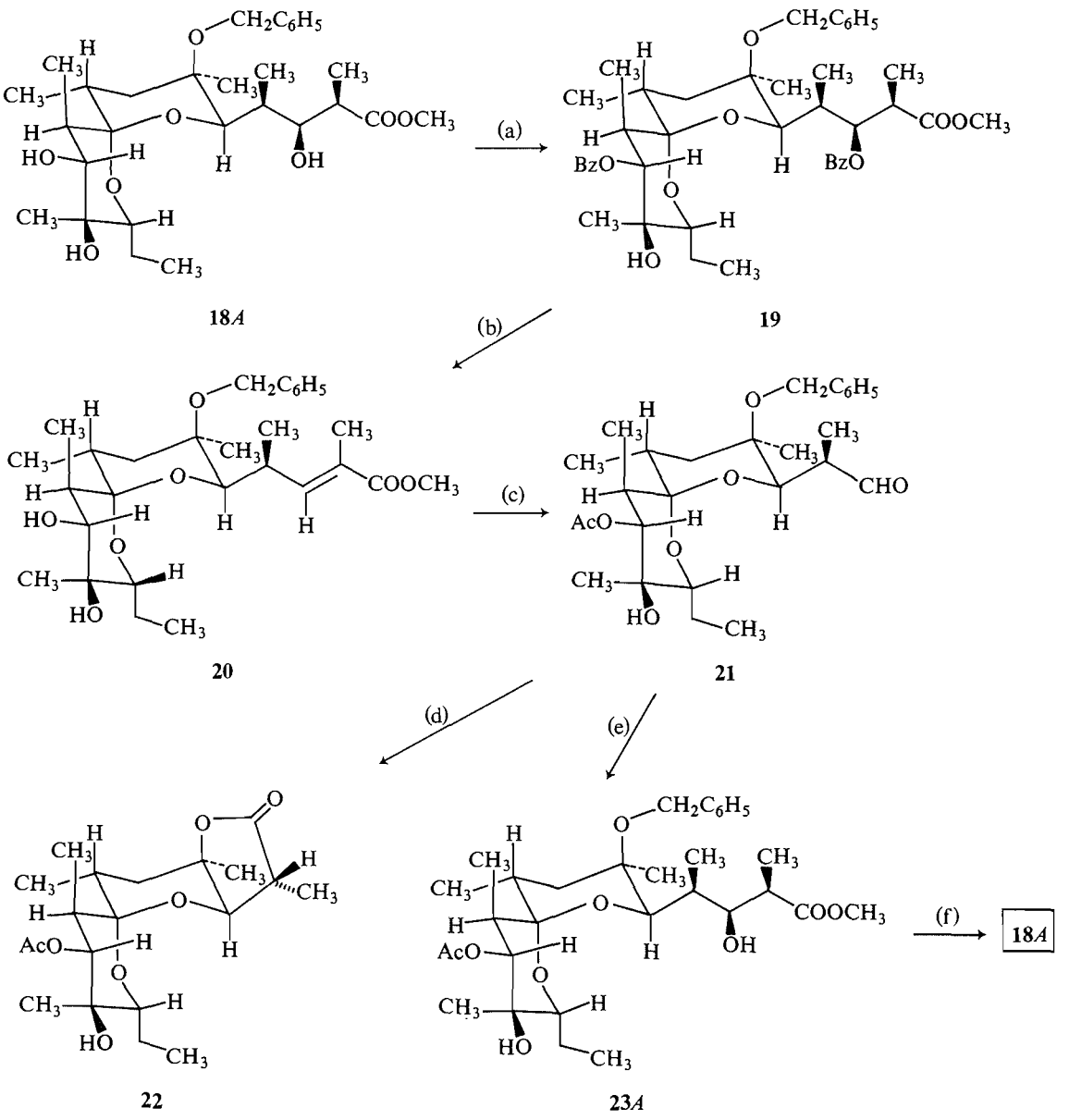
(a) H_2O_2 (3%), CH_3OH, 25°C, 24 h, 67%, ref. 2
(b) Heat at 150–155°C under vacuum, 6 h, 52%, ref. 2
(c) $NaBH_4$, isopropyl alcohol, ethyl acetate, 25°C, 2 h, 95%, ref. 2
(d) CH_3COCl (3%), CH_3OH, 25°C, 25 h, 25–65%, ref. 2
(e) 2-Methoxy propene, pyridinium tosylate, CH_2Cl_2, 25°C, 3 h, 66%, ref. 3
(f) $C_6H_5CH_2Br$, NaH, DMF, 25°C, 2.5 h, ~100%
(g) CH_3COCl (3%), CH_3OH, 25°C, 90 min, 71%
(h) HCl, acetone, Drierite, 0°C, 1 h, 95%
(i) PCC, CH_3COONa, molecular sieve 3 Å, CH_2Cl_2, 25°C, 150 min, 60%, ref. 4
(j) CH_3COOH (80%), CH_2Cl_2, ~100%

SCHEME 1



(a) CH_3ONa, CH_3OH, 25°C, 5 h, not purified
(b) CH_3COOH (80%), CH_2Cl_2, 30°C, 5 h, 70% from **8**
(c) C_6H_5OCOCl, pyridine, CH_2Cl_2, benzene, 0°C, 30 min, 82%
(d) Imidazole, toluene, 95°C → 100°C, 40 min, 98%
(e) $(CH_3CO)_2O$, $(C_2H_5)_3N$, DMAP, 25°C, 1 h, 100%
(f) $FeCl_3$, acetone, H_2O, 25°C, 15 min
(g) *p*-Toluenesulfonic acid, acetone, 25°C, 4 h, 91%
(h) K_2CO_3, CH_3OH, 25°C, 15 h, 85%

SCHEME 2



(a) C_6H_5COCl, pyridine, 70°C, 20 h, 99%
(b) CH_3ONa, CH_3OH, reflux, 2 h, 83%
(c) LAH, ether, 25°C, 90 min; $(CH_3CO)_2O$, $(C_2H_5)_3N$, DMAP, 25°C, 3 h; O_3, CH_2Cl_2, $(CH_3)_2S$, 77%
(d) Pd/C, 10%, H_2, $CH_3COOC_2H_5$, 25°C, 1 h, 100%; PCC, molecular sieve 3 Å, CH_2Cl_2, 0°C (3 min), 25°C (3 h), 100%, ref. 4
(e) $CH_3CH_2COOCH_3$, LDA, zirconocene dichloride, THF, −78°C (40 min), −78°C → −25°C (30 min), −50°C (1 h), 54%, ref. 6
(f) K_2CO_3, CH_3OH, 25°C, 1 h, 100%

SCHEME 3

C-11 phenoxycarbonate **11**, which was then transformed into the five-membered carbonate alcohol **12**. The carbonate acetate **13** obtained from **12** by acetylation yielded the substituted dihydropyran **14** on reaction with ferric chloride in wet acetone. Acetylation of **14** gave diacetate **15**. Spiroacetalization of **14** with *p*-toluenesulfonic acid in acetone gave the dioxaspiro[5.5]undecane acetate derivative **16**, having a configuration for the C-8 methyl group corresponding to that of erythromycin A. Also, on treatment with *p*-toluenesulfonic acid in acetone, 8-epi-spirocarbonate alcohol **12** can be directly converted in one step into the spirocarbonate alcohol **17**. Acetylation of **17** gave also **16**. Finally, mild basic hydrolysis of **17** with potassium carbonate in methanol provided the dioxaspiro-[5.5]undecane derivative **18*A*** (Scheme 3) of the seco acid methyl ester of erythronolide A.

Degradation of the side chain of **18*A*** was carried out in the

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*.

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[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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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-