PRACTICAL RADICAL DEOXYGENATION OF ERYTHROMYCINS BY BARTON REACTION†

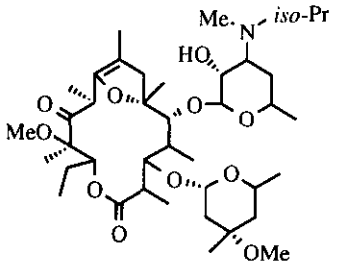
Tsutomu Sato, Hiroshi Koga*, and Koichi Tsuzuki

Fuji-gotemba Research Laboratories, Chugai Pharmaceutical Co., Ltd., 1-135, Komakado, Gotemba, Shizuoka, 412, Japan

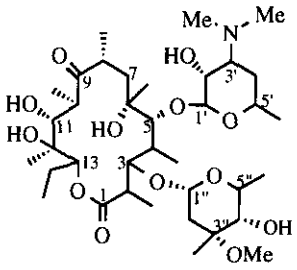
Abstract-Practical radical deoxygenation method of erythromycins was established. Macrolide-type motilin receptor agonist GM-665 (**1**) has been prepared using this method.

Motilin is a gastrointestinal peptide hormone that induces contraction of gastrointestinal tract. Thus, motilin and its receptor agonist have potential for useful prokinetic agents. GM-665 (**1**), derived from erythromycins, is a remarkably potent, orally effective motilin receptor agonist.[1] The key step of the synthesis is the deoxygenation of the 4"-OH of erythromycins, which should be carried out under mild and neutral conditions, because erythromycins are generally sensitive to acid and alkali. Barton and McCombie[2] demonstrated that alcohols can be deoxygenated in high yield by reduction of suitable thiocarbonyl derivatives at 80-100 °C with Bu_3SnH using 2,2'-azobisisobutyronitrile (AIBN) as an initiator. However, because organotin compounds are toxic and are often difficult to remove completely from the reaction products, as well as being rather costly and presenting disposal problems, various attempts using silanes,[3] dialkyl phosphites,[4] and hypophosphorous acid,[4] have been made to overcome these problems. We now wish to report the effective radical deoxygenation of erythromycins under mild conditions, practically applicable to the synthesis of GM-665 (**1**).

† This paper is dedicated to the memory of the Professor Yoshio Ban.

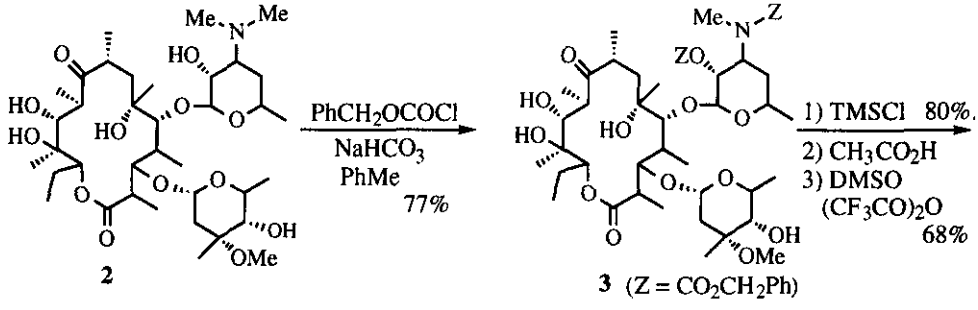


GM-665 (1)

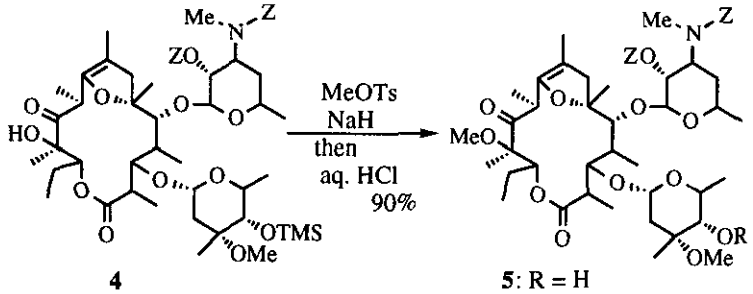


Erythromycin A (2)

Commercially available erythromycin A (**2**) was treated with benzyl chloroformate in the presence of $NaHCO_3$ in toluene to give the bis(benzyloxycarbonyl) compound (**3**) in 77% yield.[5] Silylation of the 4"-hydroxyl group of **3** (80%), followed by treatment with acetic acid and oxidation of the 11-hydroxyl group with dimethyl sulfoxide and trifluoroacetic anhydride, afforded the 11-oxo derivative (**4**) in 68% yield (2 steps). Methylation of the 12-hydroxyl group of **4** and subsequent acid treatment led to the 4"-hydroxy derivative (**5**) in 90% yield. Conversion of **5** to thiocarbonyl derivatives **6**, **7** and **8** was effected by treatment with NaH, CS_2, and MeI in DMF (73%), with 1,1'-thiocarbonyldiimidazole and 4-dimethylaminopyridine in CH_2Cl_2 (82%), and with PhNCS and NaH in THF (62%), respectively.[6]



2 **3** (Z = CO_2CH_2Ph)



4

5: R = H
6: R = C(S)SMe
7: R = C(S)imidazolyl
8: R = C(S)NHPh

These compounds (**6-8**) were applied to Barton deoxygenation reaction. The reaction of compound (**6**) with Bu_3SnH in refluxing toluene in the presence of AIBN under classical Barton-McCombie conditions[2] gave 51% of the deoxygenated product (**9**) (Table, Entry 1). The reaction of **6** with cheaper and less toxic, hypophosphorous acid and triethylamine or *N*-ethylpiperidine salt of hypophosphorous acid in refluxing dioxane in the presence of AIBN gave 68-72% of the product (**9**) (Entries 2 and 5).[4] The reduction in dimethoxyethane, MeCN, or toluene under reflux also gave similar yield of **9**, though the increased amount of AIBN was required (Entries 3, 4, and 6). On the other hand, when compound (**7**) was applied, the yield of product (**9**) was decreased (Entries 7-9). The attempted reaction of **8** gave little reduced product, the starting material being recovered (Entry 10). Thus, the best result was obtained when the reduction of substrate (**6**) was accomplished with the salts of hypophosphorous acid in boiling dioxane in the presence of AIBN (Entries 2 and 5).

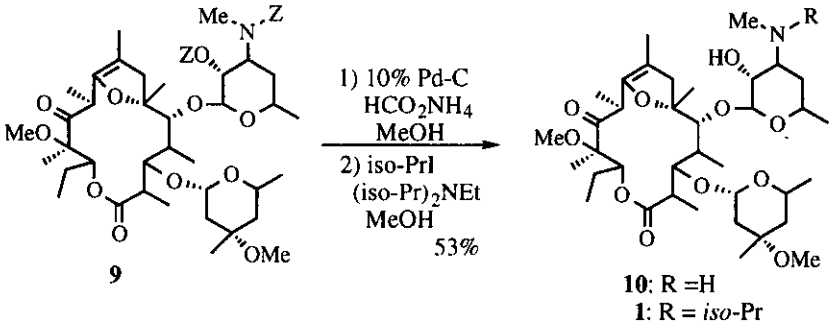
Table. Reduction of Compounds (6 - 8)

Entry	Compound	Reagent [a]	AIBN (equiv)[b]	Time (h)	Solvent (boiling)	Yield (%)[d]
1	**6**	A	0.2	1	toluene	51
2	**6**	B	0.2	1	dioxane	72
3	**6**	B	0.9	4.5	1,2-dimethoxyethane	69
4	**6**	B	1.1[c]	3	MeCN	69
5	**6**	C	0.2	1	dioxane	68
6	**6**	C	0.7	3.5	toluene	62
7	**7**	B	0.6	3	dioxane	51
8	**7**	B	1.3	8	1,2-dimethoxyethane	44
9	**7**	C	1.0	5	dioxane	35
10	**8**	B	0.5	2.5	dioxane	trace

a) A: Bu_3SnH (1.5 equiv), B: 50% H_3PO_2 aq. (5 equiv) and Et_3N (11 equiv), C. H_3PO_2•*N*-ethylpiperidine salt (5 equiv) b) AIBN (0.1 mol equiv) was added in 30 min intervals. c) AIBN (0.2 mol equiv except for the first 0.1 mol equiv) was added in 30 min intervals. d) Isolated yield.

The reduced product (**9**) was subjected to hydrogenolysis with ammonium formate and catalytic 10% Pd-C in MeOH to give the demethylated compound (**10**),[7] and *N*-alkylation of **10** with isopropyl iodide and diisopropylethylamine in MeOH afforded GM-665 (**1**) in 53% yield (2 steps).

In conclusion, deoxy erythromycin derivative GM-665 (**1**) was synthesized using Barton deoxygenation reaction. This reaction appears to be very useful for practical application to deoxygenation of erythromycins.



9

10: R =H
1: R = *iso*-Pr

ACKNOWLEDGEMENTS

The authors are grateful to Dr. M. Hamana, professor Emeritus of Kyushu University, for helpful discussions.

REFERENCES AND NOTES

1. H. Koga, T. Sato, K. Tsuzuki, and H. Takanashi, *Bioorg. Med. Chem. Lett.*, **1994**, *4* , 1649.
2. D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. I*, **1975**, 1574.
3. a) C. Chatgilialoglu, *Acc. Chem. Res.*, **1992**, *25*, 188. b) C. Chatgilialoglu, M. Guerra, A. Guerrini, G. Seconi, K. B. Clark, D. Griller, J. Kanabus-Kaminska, and J. A. Martinho-Simões, *J. Org. Chem.*, **1992**, *57*, 2427. c) C. Chatgilialoglu, A. Guerrini, and M. Lucarini, *J. Org. Chem.*, **1992**, *57*, 3405. d) D. H. R. Barton, D. O. Jang, and J. C. Jaszberenyi, *Tetrahedron*, **1993**, *49*, 7193. e) S. J. Cole, J. N. Kirwan, B. P. Roberts, and C. R. Willis, *J. Chem. Soc., Perkin Trans. I*, **1991**, 103.
4. D. H. R. Barton, D. O. Jang, and J. C. Jsazberenyi, *J. Org. Chem.*, **1993**, *58*, 6838.
5. a) E. H. Flynn, H. W. Murphy, and R. E. McMahon, *J. Am. Chem. Soc.*, **1955**, *77*, 3104.
   b) G. Kobrehel, *Japan Koukai Tokkyo Kouhou*, 5-132497 (*Chem. Abstr.*, **1992**, *117*, 70260).
6. M. Oba and K. Nishiyama, *Tetrahedron*, **1994**, *50*, 10193.
7. Y. Watanabe, M. Kashimura, T. Asaka, T. Adachi, and S. Morimoto, *Heterocycles*, **1993**, *36*, 761.

Received, 2nd June, 1995