HETEROCYCLES, Vol. 72, 2007, pp. 221 - 230. © The Japan Institute of Heterocyclic Chemistry
Received, 2nd February, 2007, Accepted, 22nd February, 2007, Published online, 23rd February, 2007. COM-07-S(K)62

RING-MEDIATED TRANSFORMATIONS OF MACROLIDE ANTIBIOTICS

Takushi Kaneko,* William McMillen,[†] Meghan Keaney Lynch,[‡] and Jon Bordner

Pfizer Global Research and Development, Groton, CT, USA 06340

Email: takushi.kaneko@pfizer.com

Current addresses:

[†] Lilly Research Laboratory, Indianapolis, IN 46245

[‡] Boston University, School of Public Health, Boston, MA 02118

Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

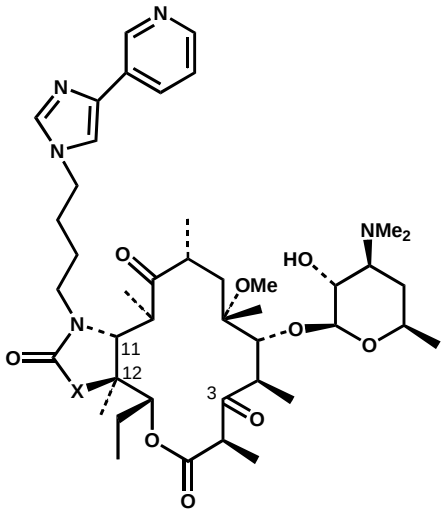
Abstract – Ketene acetal intermediate **5** was synthesized and shown to be a useful intermediate in the synthesis of macrolide antibiotics. Its synthesis and subsequent substitution reactions are controlled by the macrocyclic ring system and the juxtaposition of functional groups. The ring-mediated reactions provided unique 13- and 14-membered macrolide templates different from those available biosynthetically.

Macrolide antibiotics possessing a 14-membered lactone ring represented by erythromycin A and clarithromycin are important antibiotics against bacterial respiratory infections, but because of the emergence of resistance, newer macrolide antibiotics are urgently needed.[1]

Telithromycin (**1**) is the latest class of macrolide antibiotics generically called ketolides.[2] It is a semi-synthetic macrolide antibiotic derived from clarithromycin which shows excellent activity against

macrolide-resistant *Streptococcus pneumoniae*, macrolide-sensitive *S. aureus* and fastidious Gram-negative pathogens such as *Haemophilus influenzae*. Its structure is characterized by the presence of a keto functionality at C3, a cyclic carbamate group at C11 and C12, and a heterocycle attached at the end of a tether connected to the nitrogen atom of the cyclic carbamate moiety. When the structure of Telithromycin was first disclosed, we hypothesized that a cyclic urea analogue (**2**) might have unique antibacterial activities and PK properties because, compared with Telithromycin, it could potentially possess lower clogP, an additional hydrogen-bonding donor site, and a slightly different ring conformation. It is also important to have the capacity to generate novel ring systems with substitution patterns or ring size different from what is obtained biosynthetically.

Figure 1



1 X=O telithromycin
2 X=NH

In contemplating the syntheses of **2**, however, it was not immediately clear for us how to introduce a nitrogen atom at C12 of clarithromycin (**3**) which was a well-established starting material for ketolides.[3] The C12 position of clarithromycin is a sterically hindered tertiary alcohol and not particularly reactive. To pursue this target, we subsequently discovered that if we treated C12 imidazole carbamoyl derivative (**4**), which was a well known intermediate in ketolide chemistry,[3] with a catalytic amount of base, a unique product having an internal ketene acetal moiety (**5**) could be obtained in high yield.[4] Thus, compound **5** was obtained in approximately 70% yield when compound **4** was treated with 10 mol % of DBU in refluxing acetonitrile.[5] This product was apparently a result of the internal alkylation of C1 enolate by C12 carbon bearing a leaving group. It was also manifested by the fact that the C1-enolate group and C12 were placed in close proximity due to the 14-membered ring system. This product was crystallized from ether and hexane and its single crystal x-ray structure is shown in Figure 2. It shows a rigid bicyclic structure containing two C-C double bonds within the largest ring system and the β face of the molecule is relatively open at C9-C13.

Scheme 1

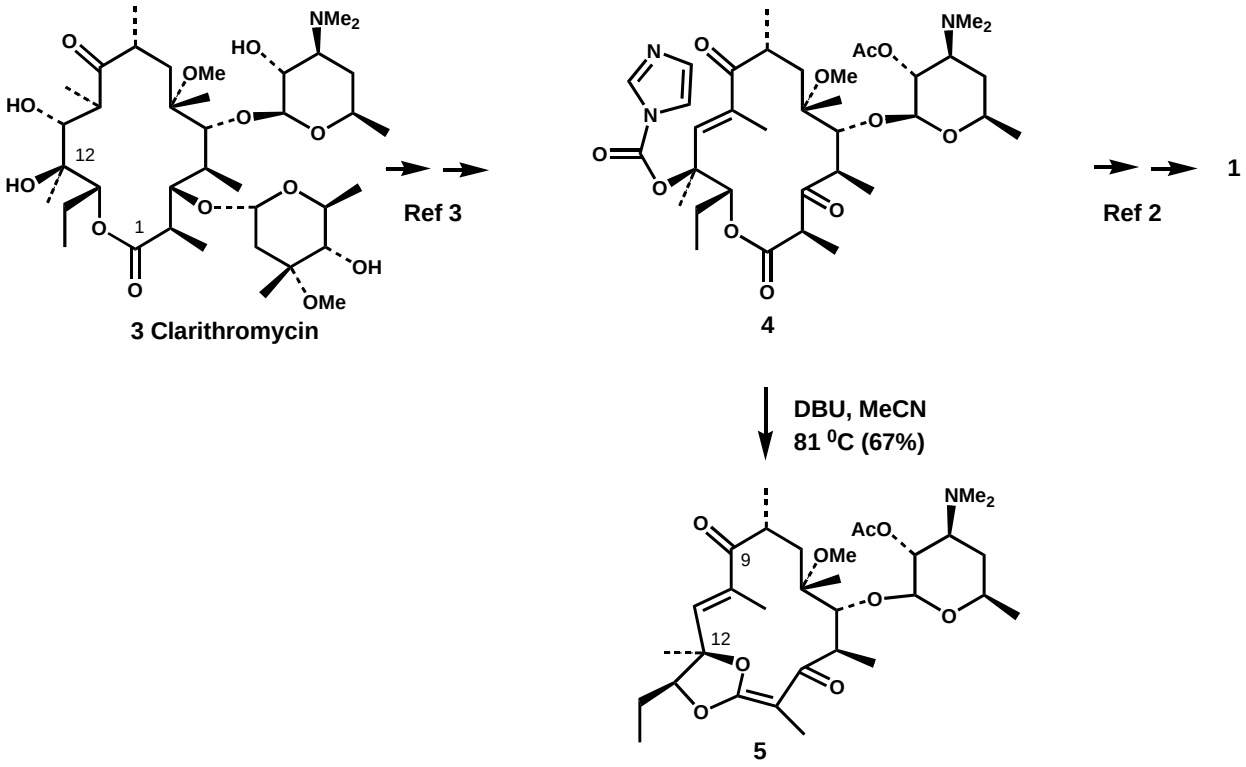
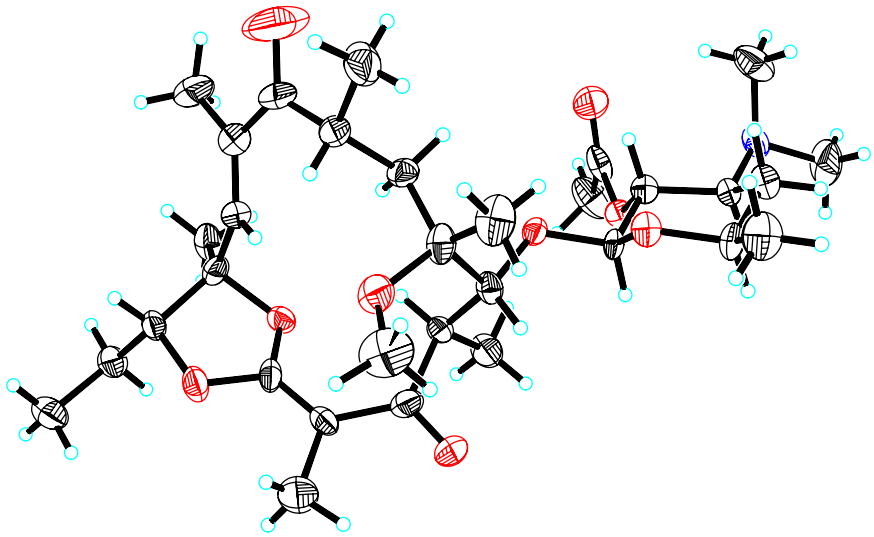


Figure 2



Since the observed product involved a modification at C12, we further envisioned that a nucleophile might add to this position if we could activate the ketene acetal moiety using Lewis acids. Indeed, when **5** was treated with 5 equivalent of trimethylsilyl azide in the presence of tin chloride (1 eq) at low temperature in dichloromethane, an azide adduct (**6**) was obtained in 69% yield.[6] By NMR and X-ray analysis (see Figure 3), the stereochemistry of the azide group was shown to be the same as the hydroxy group in clarithromycin. This stereochemistry was also predicted from the cage structure of the ketene

acetal intermediate. The stereochemistry at C2 was also the same as that of clarithromycin. Even though there were two possible sites of the ketene acetal moiety for azide to add (C12 and C13 of the original macrolide numbering system), only the C12 adduct was observed. This indicated that the product might be influenced by the allylic cation nature of the transition state.[7]

Theoretically a nucleophile attack could take place also at the allylic position (that is, at C10 rather than C12). When ketene acetal **5** was treated with 1 equivalent of yttrium triflate and 5 equivalents of trimethylsily cyanide at 60 °C in acetonitrile, new product **7** was obtained in 68% yield.[8, 910] The stereochemistry of the cyanide group is presumed to be as drawn based on the structure of **5**. Furthermore, if ketene acetal **5** was treated with trimethylsily cyanide in the presence of excess tetrabutylammonium fluoride in THF at 80 °C, yet another ring system **8** was obtained in 53% yield.[11] This structure was also established by X-ray (see Figure 4). The structure showed that the C-C double bond is in a trans configuration and the ring conformation is quite different from that of **6**. The formation of this can be rationalized by initial addition of the cyanide at C11,[12] followed by deprotonation at C11 and opening of the ketene acetal moiety (see **9**).

Scheme 2

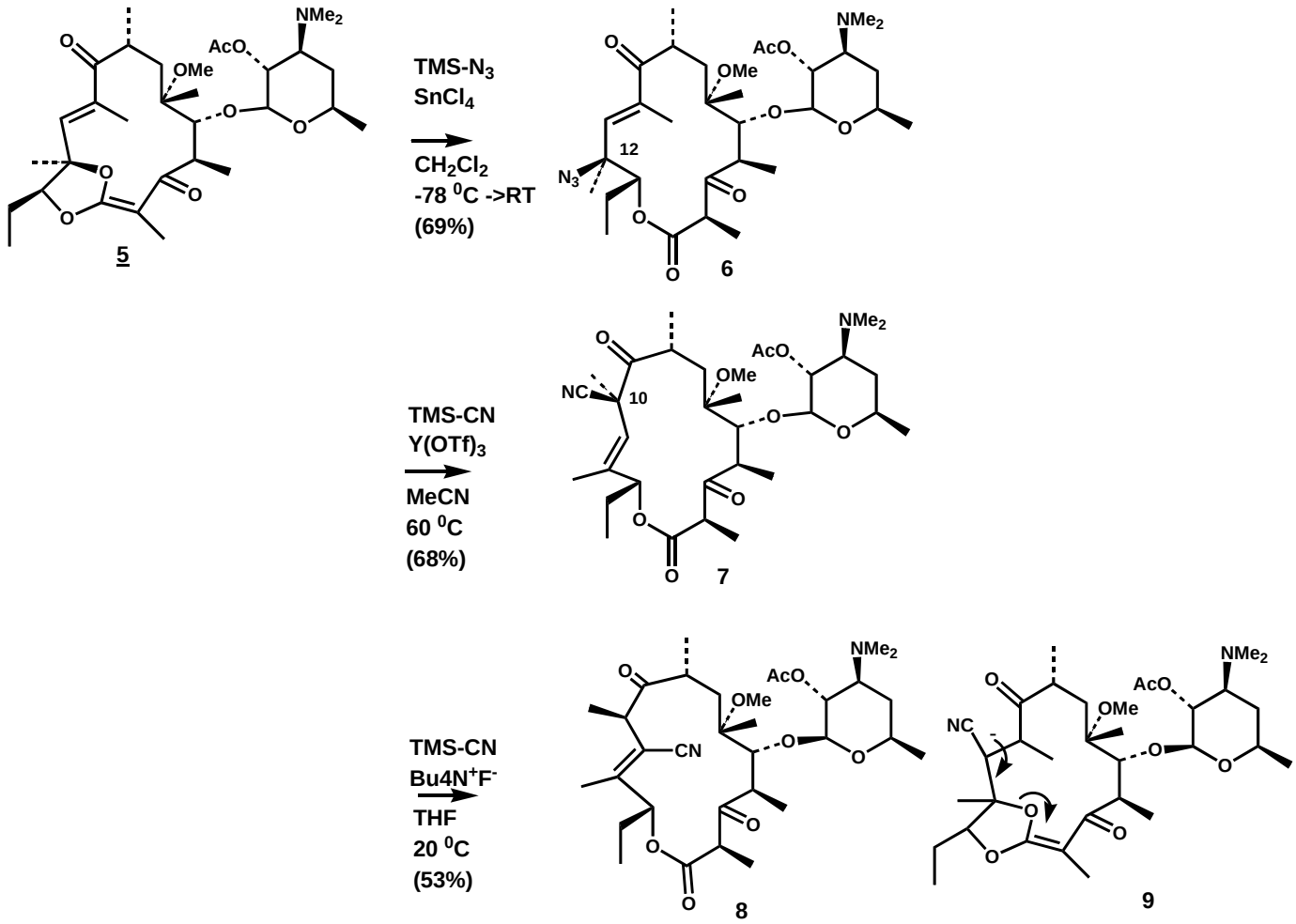


Figure 3

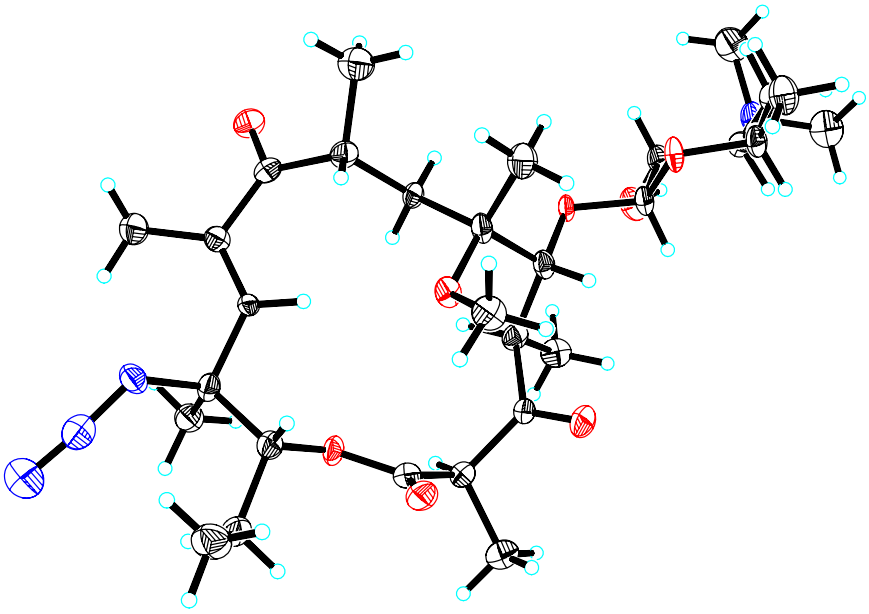
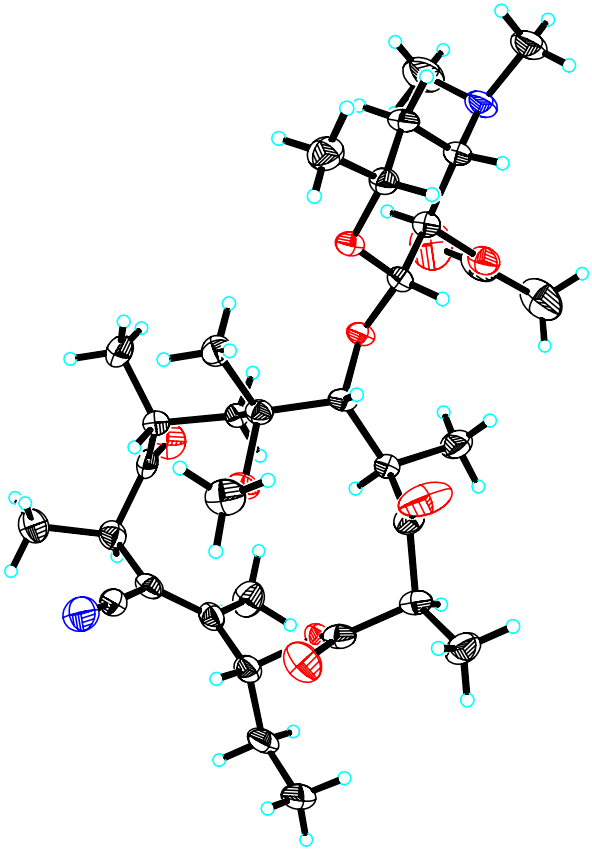


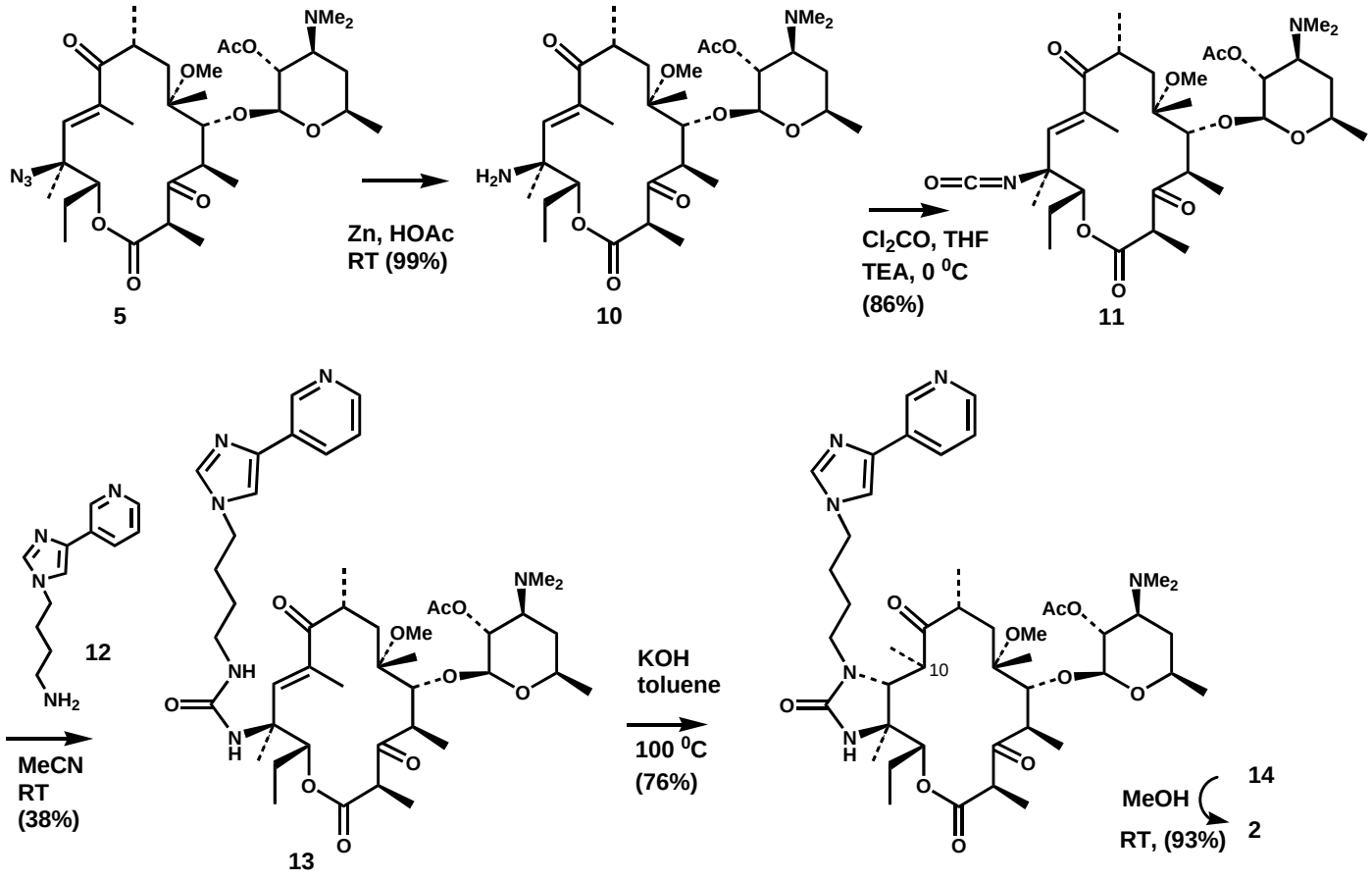
Figure 4



In the pursuit of original cyclic urea analogue, reduction of azide to amine without reducing the enone

moiety in **6** was best carried out using zinc and acetic acid since catalytic hydrogenation was somewhat erratic.[13] Thus, azide was treated with zinc in acetic acid at room temperature for 45 min to provide amine **10** in almost quantitative yield.[14] The resulting amine was used without further purification in its conversion to isocyanate **11**[15] by treating at 0 °C with 2 equivalents of phosgene in THF in the presence of excess TEA for 45 min. The isocyanate intermediate was allowed to react at room temperature with amine **12** to provide urea **13** in 38% yield.[16,17] In contrast to the carbamate derivative which cyclized to the eneone system under the condition of its formation,[2] the urea derivative was obtained as an open isomer (**13**). Cyclization was achieved by treating the open isomer with catalytic KOH in toluene at 100 °C for 1.2 hrs. In the cyclic urea product (**14**),[18] the C10-H appeared as a singlet at δ 3.11 similar to that observed with cyclic carbamate structures[19], establishing its stereochemistry as in the β face. The acetyl group at C2' was removed by warming in MeOH to give the desired product **2**.[20] In this fashion the desired cyclic urea congener of telithromycin was synthesized. The product and its analogues exhibited antibacterial activity comparable or better than that of telithromycin, and it will be reported elsewhere.

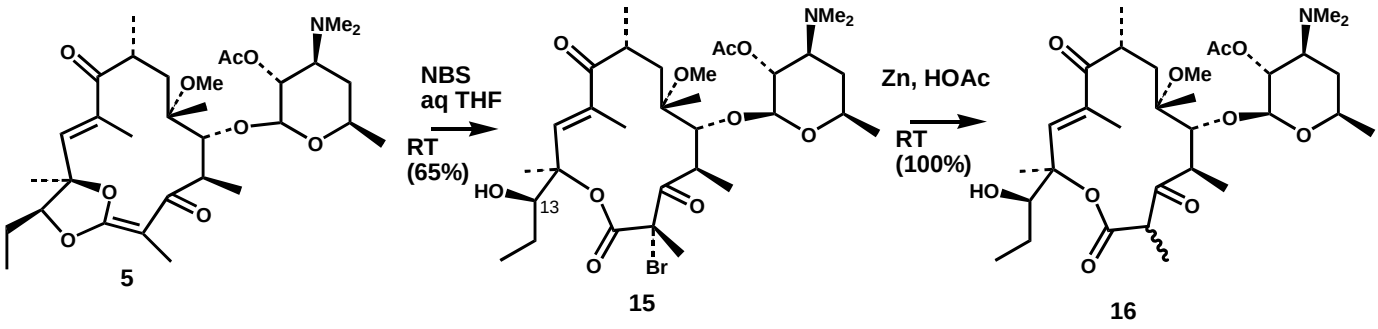
Scheme 3



The ketene acetal intermediate has many other possibilities of transformation. Ketene acetals are known to react with bromine.[21] When ketene acetal **5** was allowed to react with NBS in water, we generated yet

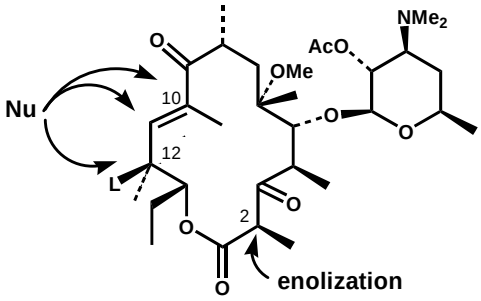
another ring system. Thus, treatment with 1 equivalent of NBS in aqueous THF at room temperature for 1 hr, a new ring system with a 13-membered lactone **15** was obtained.[22] In this product C13 proton appears at δ 3.49 which is quite different from 14-memebered lactone case (δ 4.8-5.9). This was rationalized by an addition of bromonium ion to the ketene moiety and hydrolysis of the subsequent orthoester. The bromine atom in **15** was further reduced by Zn in AcOH at room temperature for 30 min to give **16**.[23] In these transformations the original 14-membered macrolide was transformed into a 13-membered macrolide with the original carbonyl oxygen atom ending up as a ring oxygen, providing ring systems different from those in natural products. For the purpose of drug discovery it is important to have the ability to alter substitution patterns and the ring size of macrolide antibiotics.

Scheme 4



As mentioned briefly above, some nucleophiles add at C10 as well as at C12 in the Lewis acid-catalyzed reactions with the ketene acetal intermediate. Etiologically, this ketene acetal intermediate is formed by enolization at C2, and in the subsequent nucloephile addition reactions substitutions take place at positions 5- (that is, at C12) or 7-atoms (at C10) away from the original site of enolization (see **17**). These observations can be considered similar to examples of anchimeric assistance in solvolysis reactions except in this case it goes through isolable intermediates and distinct reaction steps. Thus, the substitution at C12 takes place at this sterically congested center bearing a leaving group with retention of configuration. The ring system and the juxtaposition of functional groups are considered to be responsible for these transformations at remote sites. The size of the ring must also be important to have sufficient flexibility for the interacting groups to come close and at the same time to avoid the strain of a bridge-head double bond. It may be of interest to investigate further scope and limitation of this type of remote-site functionalization in other ring systems.

Figure 5



17

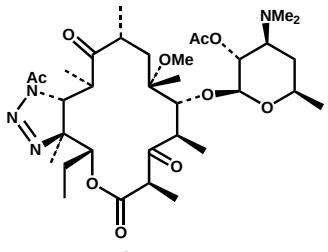
ACKNOWLEDGEMENTS

We thank Diane Rescek and Melissa Lin for their extensive NMR work.

REFERENCES AND NOTES

1. T. Kaneko, T. J. Dougherty, and T. V. Magee, 'Comprehensive Medicinal Chemistry II,' Vol. 7, ed. by D. J. Triggle and J. B. Taylor, Elsevier, Oxford, 2006, pp. 519-566.
2. A. Denis, C. Agouridas, J.-M. Auger, Y. Benedetti, A. Bonnefoy, F. Bretin, J.-F. Chantot, A. Dussarat, C. Fromentin, S. G. D'Ambrieres, S. Lachaud, P. Laurin, O. Le Martret, V. Loyau, N. Tessot, J.-M. Pejac, and S. Perron, *Bioorg. Med. Chem. Letters*, 1999, **9**, 3075.
3. C. Agouridas, A. Denis, J.-M. Auger, Y. Benedetti, A. Bonnefoy, F. Bretin, J.-F. Chantot, A. Dussarat, C. Fromentin, S. G. D'Ambrieres, S. Lachaud, P. Laurin, O. L. Martret, V. Loyau, and N. Tessot, *J. Med. Chem*., 1998, **41**, 4080.
4. Selected data for **5**: ^{1}H NMR ($CDCl_3$) δ 6.32 (s, 1H, C11-H); 4.68 (dd, J=10.5, 7.7 Hz, 1H, C1'-H), 4.28 (dd, J=9.1, 4.9 Hz, 1H, C13-H), 4.03 (d, J=9.6 Hz, 1H, C5-H), 3.90 (m, 1H, C4-H), 3.46 (m, 1H, C5'-H), 3.19 (m, 1H, C8-H), 2.85 (s, 3H, OMe), 2.64 (m, 1H, C3'-H), 2.22 (s, 6H, NMe_2), 2.13 (dd, J=5.0, 3.1 Hz, 1H, C7-H), 2.03 (s, 3H, AcO), 1.92 (s, 3H, C10-Me), 1.74 (s, 3H, C12-Me), 1.73 (s, 3H, C2-Me), 1.65 (m, 2H, C4'-H and C14-H), 1.30 (s, 3H, C6-Me), 1.23 (m. 2H, C7, C4'-H), 1.18 (d, 3H, J= 6.2 Hz, C5'-Me), 1.13 (d, J=6.2 Hz, 3H, C8-Me), 1.10 (t, J= 7.5 Hz, 3H, C14-Me), 1.1 (m, 1H, C14-H), 1.09 (d, J=7.1, 3H, C8-Me), 1.02 (d, J=7.1, 3H, C4-Me); MS m/z 594 (M+1).
5. In addition, there was a minor product in which the methyl group at C8 was epimerized (18% Yield). ^{1}H NMR ($CDCl_3$) δ 6.01 (s, 1H, C11-H), 4,76 (t, J=9 Hz, 1H, C1'-H), 4.48 (m, 2H, C13, C1'-H), 3.91 (d, 1H, J=9.1Hz, C5-H), 3.65 (m, 1H, C4-H), 3.51 (m, 1H, C5'-H), 3.25 (m, 1H, C8-H), 2.76 (s, 3H, OMe), 2.71 (m, 1H, C3'-H), 2.24 (s, 6H, NMe_2), 2.06 (s, 3H, AcO), 2.02 (s, 3H, C10-Me), 1.89 (m, 1H, C7-H), 1.69 (s, 3H, Me), 1.65 (s, 3H, Me), 1.59 (m, 2H, C14-H, C4'-H), 1.30 (m, 1H, C7-H), 1.22 (s, 3H, Me), 1.16-1.07 (m, 13H); MS m/z 594 (M+1).
6. Selected data for **6**: ^{1}H NMR ($CDCl_3$) δ 6.38 (s, 1H, C11-H), 5.08 (dd, J=2.5, 0.8 Hz, 1H, C13-H), 4.70 (dd, J=10.6, 7.6 Hz, 1H, C2'-H), 4.31 (d, J=7.5 Hz, 1H, C1'-H), 4.05 (d, J=8.3 Hz, 1H, C5-H), 3.60 (q, J=7.1 Hz, 1H, C2-H), 3.50 (m, 1H, C5'-H), 3.10 (m, 1H, C8-H), 2.95 (m, 1H, C4-H), 2.76 (s, 3H, OMe), 2.60 (m, 1H, C3'-H), 2.21 (s, 6H, NMe_2), 2.03 (s, 3H, OAc), 1.98 (s, 3H, C10-Me), 1.87 (m, 1H, C14-H), 1.9-1.6 (m, 2H, C7-H), 1.69 (m, 1H, C4'-H), 1.5 (m,1H, C14-H), 1.54 (s, 3H, C12-Me), 1.49 (s, 3H, C12-Me), 1.33 (d, J=7.1 Hz, 3H, C2-Me), 1.27 (s, 3H, C6-Me), 1.25 (m, 1H, C4'-H), 1.21 (d, J= 6.2 Hz, 3H, C5'-Me), 1.17 (d, J=6.6 Hz, 3H, C8-Me), 1.09 (d, J=7.3 Hz, 3H, C4-Me), 0.91 (t, J=7.3 Hz, 3H, C14-Me); IR 2105 cm^{-1} (N_3); MS m/z 637 (M+1).
7. The initial reaction product was actually enol silyl ether at C3 as shown by its NMR and MS.

8. Selected data for **7**: ^{1}H NMR ($CDCl_3$) δ 5.50 (s, 1H, C11-H), 5.11 (t, J=6.6 Hz, 1H, C13-H), 4.74 (dd, J=10.4, 7.5 Hz, 1H, C2'-H), 4.29 (d, J= 7.5 Hz, 1H, C1'-H), 4.04 (d, J=9.1 Hz, 1H, C5-H), 3.55 (q, J= 7.06 Hz, 1H, C2-H), 3.47 (m, 1H, C5'-H), 2.86 (m, 1H, C4-H), 2.82 (s, 3H, OMe), 2.63 (m, 1H, C3'-H), 2.22 (s, 6H, NMe_2), 2.01 (s, 3H, OAc), 1.73 (s, 3H, C12-Me), 1.66 (s, 3H, C10-Me), 1.7-1.5 (m, 3H, C4'-H, C14-H, C7-H), 1.5-1.3 (m, 3H, C7-H, C14-H, C4'-H), 1.36 (s, 3H, C6-Me), 1.24 (d, J=7.1 Hz, 1H, C2-Me) 1.21 (d, J= 5.8 Hz, 1H, C5'-Me), 1.16 (d, J= 6.6 Hz, 1H, C8-Me), 1.14 (d, J=7.5 Hz, 1H, C4-Me) 0.86 (t, 3H, C14-Me); MS m/z 621 (M+1).
9. Scandium triflate can be also used.
10. As one of the referees suggested, we had considered the formation of **6** as the result of an allylic rearrangement of the C10-azide intermediate. At present we do not have data to confirm or rule out this possibility.
11. Selected data for **8**: ^{1}H NMR ($CDCl_3$) δ 5.99 (t, J= 7.1 Hz, 1H, C13-H), 4.70 (dd, J=10.8, 7.9 Hz, 1H, C2'-H), 4.42 (d, J= 7.9 Hz, 1H, C1'-H), 4.15 (d, J= 4.2 Hz, 1H, C5-H), 3.72 (q, J= 7.1 Hz, 1H, C2-H), 3.57 (m, 1H, C10-H), 3.54 (m, 1H, C5'-H), 3.03 (m, 1H, C4-H), 2.80 (s, 3H, OMe), 2.76 (m, 1H, C8-H), 2.22 (s, 6H, NMe_2), 1.98 (s, 3H, OAc), 1.92 (s, 3H, C12-Me), 1.81 (m, 1H, C14-H), 1.71 (m, 1H, C4'-H), 1.65 (m, 1H, C14-H), 1.45 (m, 1H, C7-H), 1.31 (d, J= 7.6 Hz, 3H, C10-Me), 1.24 (d, J=6.6 Hz, 3H, C2-Me), 1.21 (d, J=6 Hz, 3H, C5'-Me), 1.11 (d, J= 7.1 Hz, 1H, C8-Me), 1.05 (d, J= 7.9 Hz, 3H, C4-Me) 0.86 (t, J= 7.5Hz, 3H, C14-Me); MS m/z 621 (M+1).
12. Thiols, alcohols, or amines can add at the C11 in a Michael addition fashion.
13. Hydrogenation using Lindlar's catalyst or triethyl phosphine reduction of **6** sometimes gave a partially reduced cyclized product as characterized by its acetylated derivative (structure **A**); ^{1}H NMR ($CDCl_3$) δ 4.76 (dd, J=10.4, 7.5 Hz, 1H, C2'-H), 4.37 (dd, J= 10.0, 2.5 Hz, 1H, C13-H), 4.33 (d, J= 10.4 Hz, 1H, C1'-H), 4.06 (d, J=9.1 Hz, 1H, C5-H), 3.92 (s, 1H, C11-H), 3.83 (q, J= 7.3 Hz, 1H, C2-H), 3.76 (m, 1H, C10-H), 3.50 (m, 1H, C5'-H), 3.10 (q, J=7.5 Hz, 1H, C4-H), 2.87 (m, 1H, C3'-H), 2.79 (s, 3H, OMe), 2.70 (m, 1H, C8-H), 2.31 (s, 6H, NMe_2), 2.16 (m, 1H, C7-H), 2.06 (s, 3H, Ac), 1.99 (s, 3H, Ac), 1.82 (m, 2H, C14-H, C4'-H), 1.78 (s, 3H, C12-Me), 1.38 (d, J= 7.1 Hz, 1H, C2-Me), 1.30 (m, 2H, C7-H, C4'-H), 1.21 (m, 6H, C4-Me, C5'-Me), 1.12 (s, 3H, C6-Me), 0.95 (d, J= 7.9 Hz, 3H, C8-Me), 0.93 (d, J=7.9 Hz, 3H, C10-Me), 0.79 (t, J= 7.5 Hz, 3H, C14-Me); MS m/z 681 (M+1).



A

14. Selected data for **10**: ^{1}H NMR ($CDCl_3$) δ 6.57 (s, 1H, C11-H), 4.95 (d, J= 7.9 Hz, 1H, C13-H), 4.80 (m, 1H, C2'-H), 4.33 (d, J= 7.7 Hz, 1H, C1'-H), 4.09 (d, J= 7.5 Hz, 1H, C5-H), 3.67 (q, J= 6.8 Hz, 1H, C2-H), 3.60 (m, 1H, C5'-H), 3.15 (m, 1H, C8-H), 3.02 (m, 1H, C4-H), 2.89 (s, 3H, OMe), 2.65 (m, 1H, C3'-H), 2.22 (s, 6H, NMe_2), 2.03 (s, 3H, OAc), 2.00 (s, 3H, C10-Me), 1.9 (m, 1H, C14-H), 1.7-1.5 (m, 3H, C7-H, C14-H, C4'-H), 1.37 (m, 6H, C6-Me, C12-Me), 1.32 (m, 6H, C2-Me, C5'-Me), 1.3-1.1 (m, 2H, C7-H, C4'-H), 1.08 (m, 6H, C4-Me, C8-Me), 0.90 (t, J= 7.5 Hz, 3H, C14-Me); MS m/z 611 (M+1). This was used directly in the next step.
15. Selected data for **11**: ^{1}H NMR ($CDCl_3$) δ 6.48 (s, 1H, C11-H), 5.10 (dd, J=7.1, 2.9 Hz, 1H, C13-H), 4.77 (m, 1H, C2'-H), 4.38 (d, J= 7.5 Hz, 1H, C1'-H), 4.14 (m, 1H, C5-H), 3.74 (q, J= 6.9 Hz, C2-H), 3.57 (m, 1H, C5'-H), 3.17 (m, 1H, C8-H), 3.04 (m, 1H, C4-H), 2.83 (bs, 3H, OMe), 2.69 (m, 1H, C3'-H), 2.29 (bs, 6H, NMe_2), 2.10 (bs, 3H, OAc), 2.06 (s, 3H, C10-Me), 1.96 (m, 1H, C14-H), 1.71 (m, 1H, C4'-H), 1.7-1.1 (m, 4H, C7-H, C14-H, C4'-H), 1.60 (s, 3H, C12-Me), 1.34 (d, J= 7.6 Hz, 3H, C2-Me), 1.26 (s, 3H, C6-Me), 1.24 (d, J= 7.6 Hz, 3H, C5'-Me), 1.18 (d, J= 6.6 Hz,

3H, C8-Me), 1.09 (d, J= 7.6 Hz, 3H, C4-Me), 0.93 (t, J= 7.5 Hz, C14-Me); IR 2257 cm^{-1}; MS m/z 637 (M+1).

16. Selected data for **13**: ^{1}H NMR ($CDCl_3$) δ 8.96 (s, 1H, Py-2H), 8.46 (dd, J=4.8, 1.5 Hz, 1H, Py-6H), 8.07 (d, J= 7.8 Hz, 1H, Py-4H), 7.50 (s, 1H, Im-2H), 7.30 (m, 1H, Py-5H), 7.29 (s, 1H, Im-5H), 6.80 (s, 1H, C11-H), 5.57 (dd, J=8.4, 1.8 Hz, 1H, C13-H), 5.11 (s, 1H, NH), 4.96 (s, 1H, NH), 4.69 (dd, J=10.3, 7.7 Hz, 1H, C2'-H), 4.32 (d, J=7.3 Hz, 1H, C1'-H), 4.12 (d, J=8.4 Hz, 1H, C5-H), 3.98 (t, J=7.0 Hz, 2H, CH_2), 3.72 (q, J=6.9 Hz, 1H, C2-H), 3.53 (m, 1H, C5'-H), 3.35 (m, 1H, C8-H), 3.17 (m, 2H, CH_2), 3.07 (m, 1H, C4-H), 2.96 (s, 3H, OMe), 2.64 (m, 1H, C3'-H), 2.22 (s, 6H, NMe_2), 2.01 (s, 3H, OAc), 1.88 (s, 3H, C10-Me), 1.77 (m, 2H, C7-H and C14-H), 1.70 (m, 1H, C4'-H), 1.46 (m, 2H, C7-H and C14-H), 1.45 (m, 2H, CH_2), 1.39 (s, 3H, C12-Me), 1.34 (d, J=6.6 Hz, 3H, C2-Me), 1.33 (s, 3H, C6-Me), 1.30 (m, 1H, C4'-H), 1.24 (d, J=6.2 Hz, C5'-Me), 1.09 (d, J=7.0 Hz, C8-Me), 1.08 (d, J=7.0 Hz, C4-Me), 0.89 (t, J=7.5 Hz, 3H, C14-Me); MS m/z 853 (M+1).
17. We could not affect addition of trimethylsilyl isocyanate to the ketene acetal intermediate which would have given the advanced intermediate **11** directly.
18. Selected data for **14**: ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1H, Py-2H), 8.43 (bs, 1H, Py-6H), 8.06 (m, 1H, Py-4H), 7.53 (m, 1H, Im-2H), 7.31 (s, 1H, Im-H), 7.27 (m, 1H, Py-3H), 4.91 (s, 1H, NH), 4.86 (m, 1H, C13-H), 4.84 (m, 1H, C2'-H), 4.37 (d, J= 7.5 Hz, 1H, C1'-H), 4.19 (d, J=8.4 Hz, 1H, C5-H), 3.98 (t, J=6.8 Hz, 2H, CH_2), 3.80 (q, J= 6.8 Hz, 1H, C2-H), 3.62 (m, 1H, C8-H), 3.6 (m, 2H, CH_2), 3.57 (m, 1H, C5'-H), 3.44 (s, 1H, C11-H), 3.09 (m, 1H, C10-H), 3.03 (m, 1H, C4-H), 2.59 (s, 3H, OMe), 2.5 (m, 1H, C3'-H), 2.40 (bs, 6H, NMe_2), 2.14 (bs, 3H, OAc), 1.85 (m, 1H, C14-H), 1.82 (m, 2H, CH_2), 1.80 (d, J= Hz, 1H, C8-Me), 1.6 (m, 3H, C7-H, C14-H and C4'-H), 1.50 (m, 1H, CH_2), 1.4 (m, 3H, C7-H, C14-H and C4'-H), 1.3-1.2 (m, 12H, C2-Me, C6-Me, C12-Me, and C5'-Me), 1.11 (d, J=7.9 Hz, 3H, C4-Me), 1.00 (d, J= 6.6 Hz, 3H, C10-Me), 0.76 (t, J= 7.1 Hz, 3H, C14-Me); MS m/z 853 (M+1).
19. W. R. Baker, J. Clark, R. L. Stephens, and K. H. Kim, *J. Org. Chem*., 1988, **53**, 2340.
20. Selected data for **2**: ^{1}H NMR ($CDCl_3$) δ 8.94 (bs, 1H, Py-2H), 8.43 (bs, 1H, Py-6H), 8.06 (d, J= 7.7 Hz, 1H, Py-4H), 7.53 (m, 1H, Im-2H), 7.33 (s, 1H, Im-H), 7.28 (m, 1H, Py-3H), 4.86 (m, 1H, C13-H), 4.76 (s, 1H, NH), 4.30 (d, J= 7.0 Hz, 1H, C1'-H), 4.21 (d, J=8.7 Hz, 1H, C5-H), 3.98 (t, J=7.2 Hz, 2H, CH_2), 3.83 (q, J=6.9 Hz, 1H, C2-H), 3.70 (q, J= 7.1 Hz, 1H, C8-H), 3.6 (m, 2H, CH_2), 3.57 (m, 1H, C5'-H), 3.44 (s, 1H, C11-H), 3.35 (t, J=7.4 Hz, 1H, C2'-H), 3.10 (m, 1H, C10-H), 3.08 (m, 1H, C4-H), 2.61 (s, 3H, OMe), 2.5 (m, 1H, C3'-H), 2.46 (bs, 6H, NMe_2), 1.85 (m, 1H, C14-H), 1.83 (m, 2H, CH_2), 1.80 (m 1H, C8-Me), 1.76-1.40 (m, 6H, C7-H, C14-H and C4'-H), 1.61 (m, 1H, CH_2), 1.3-1.2 (m, 12H, C2-Me, C6-Me, C12-Me, and C5'-Me), 1.11 (d, J=6.8 Hz, 3H, C4-Me), 1.02 (d, J= 6.8 Hz, 3H, C10-Me), 0.80 (t, J= 7.3 Hz, 3H, C14-Me); MS m/z 811 (M+1).
21. S. M. McElvain and R. E. Starn, *J. Am. Chem. Soc*., 1955, **77**, 4571.
22. Selected data for **15**: ^{1}H NMR ($CDCl_3$) δ 6.84 (s, 1H, C11-H), 4.73 (dd, J=10.4, 7.5 Hz, 1H, C2'-H), 4.41 (d, J=7.5Hz, 1H, C1'-H), 3.86 (m, 1H, C5-H), 3.82 (q, J=6.2 Hz, 1H, C4-H), 3.49 (m, 2H, C5'-H and C13-H), 2.96 (m, 1H, C8-H), 2.87 (s, 3H, OMe), 2.79 (m, 1H, C3'-H), 2.30 (s, 6H, NMe_2), 2.06 (s, 3H, OAc), 1.97 (s, 3H, C2-Me), 1.87 (s, 3H, C10-Me), 1.82 (s, 3H, C12-Me), 1.81 (m, 1H, C4'-H), 1.77 (m, 1H, C7-H), 1.52 (d, J=6.2 Hz, 1H, C4-Me), 1.44 (m, 1H, C14-H), 1.34 (m, 1H, C14-H), 1.33 (m, 1H, C4'-H), 1.29 (s, 3H, C6-Me), 1.24 (m, 1H, C7-H), 1.21 (d, J=5.8 Hz, 3H, C5'-Me), 1.11 (d, J=6.6 Hz, C8-Me), 1.01 (t, J=7.06 Hz, C14-Me); MS m/z 690 (M+1).
23. Selected data for **16**: ^{1}H NMR ($CDCl_3$) δ 6.97 (s, 1H, C11-H), 4.74 (dd, J=10.4, 7.5 Hz, 1H, C2'-H), 3.97 (d, J=10.8 Hz, 1H, C5-H), 3.65 (m, 1H, C4-H), 3.51 (m,1H, C5'-H), 3.44 (m, 2H, C2-H and C13-H), 3.01 (m, 1H, C8-H), 2.88 (s, 3H, OMe), 2.75 (m, 1H, C3'-H), 2.89 (s, 6H, NMe_2), 2.05 (s, 3H, OAc), 1.99 (m, 1H, C7-H), 1.88 (s, 3H, C10-Me), 1.79 (m, 3H, C7-H, C14-H and C4'-H), 1.78 (s, 3H, C12-Me), 1.38 (m, 3H, C7-H, C14-H, and C4'-H), 1.28 (s, 3H, C6-Me), 1.22 (m, 6H, C2-Me and C5'-Me), 1.11 (m, 6H, C4-Me and C8-Me), 1.00 (t, J= Hz, 3H, C14-Me); MS m/z 612 (M+1).