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Synthetic studies toward C-1027 chromophore: construction of a highly unsaturated macrocycle

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Abstract—Construction of the highly unsaturated macrolactone of C-1027 chromophore (**1**) was investigated. Coupling of three fragments (**2**, **3**, **4**) led to the *seco*-acids in a concise manner. The protecting groups on the *seco*-acids influenced the yield of macrolactonization, and efficient conversion from acetonide **13** to lactone **15** was achieved using the Corey–Nicolaou protocol. The desired atropisomer thus obtained was converted to triol **18a**, which will serve as an important intermediate in the total synthesis of C-1027 chromophore. © 2001 Elsevier Science Ltd. All rights reserved.

In 1989, Otani and co-workers isolated the extremely potent antitumor chromoprotein antibiotic C-1027[1] from the culture broth of *S. globisporus* C-1027.[2] The structure elucidation revealed that this compound is one of the family of chromoproteins[3] which contain a carrier apoprotein and a highly unstable chromophore.[4] While C-1027 chromophore (**1**, Fig. 1) is reasonably stable when bound to apoprotein, **1** in its free form smoothly aromatizes via a Masamune–Bergman rearrangement even at room temperature.[4b] Through this rearrangement, **1** exerts its activity by abstracting hydrogen from the backbone of DNA, resulting in double strand cleavage.[5] Our own studies suggested that the nine-membered enediyne is in equibrium with parabenzyne,[6] which is kinetically stabilized by the apoprotein.[7] Its potent biological activity and interesting physicochemical property, as well as the highly complex architecture attracted us to the chemical synthesis of this compound.[8] In previous studies toward total synthesis, we efficiently constructed the nine-membered ring[9] and aryl ether,[10] and achieved highly selective glycosylation of the tertiary alcohol.[11] In this paper, we demonstrate the successful construction of the highly unsaturated 17-membered macrolide by lactonization of a strategically protected *seco*-acid.

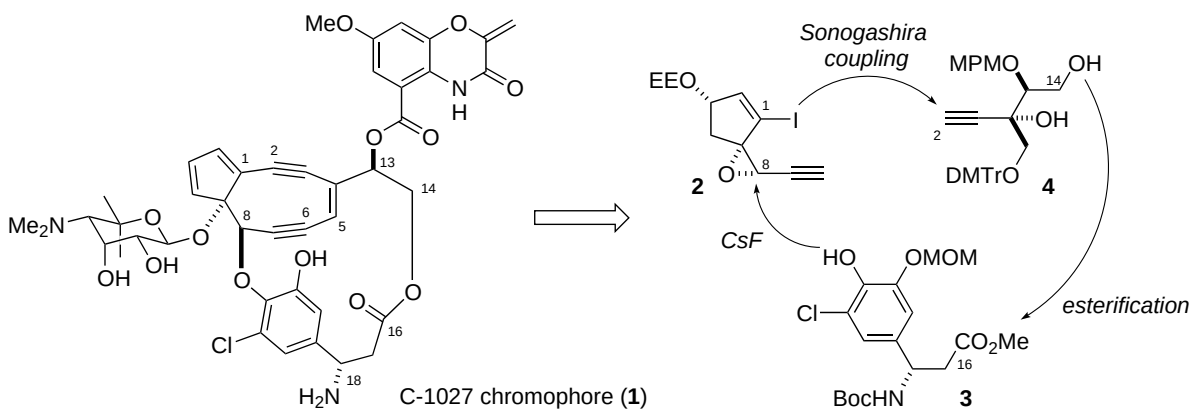

Figure 1. Structure and retrosynthetic analysis of C-1027 chromophore (**1**).

Keywords: C-1027; enediyne; chromoprotein antibiotics; macrolactonization; Sonogashira coupling.
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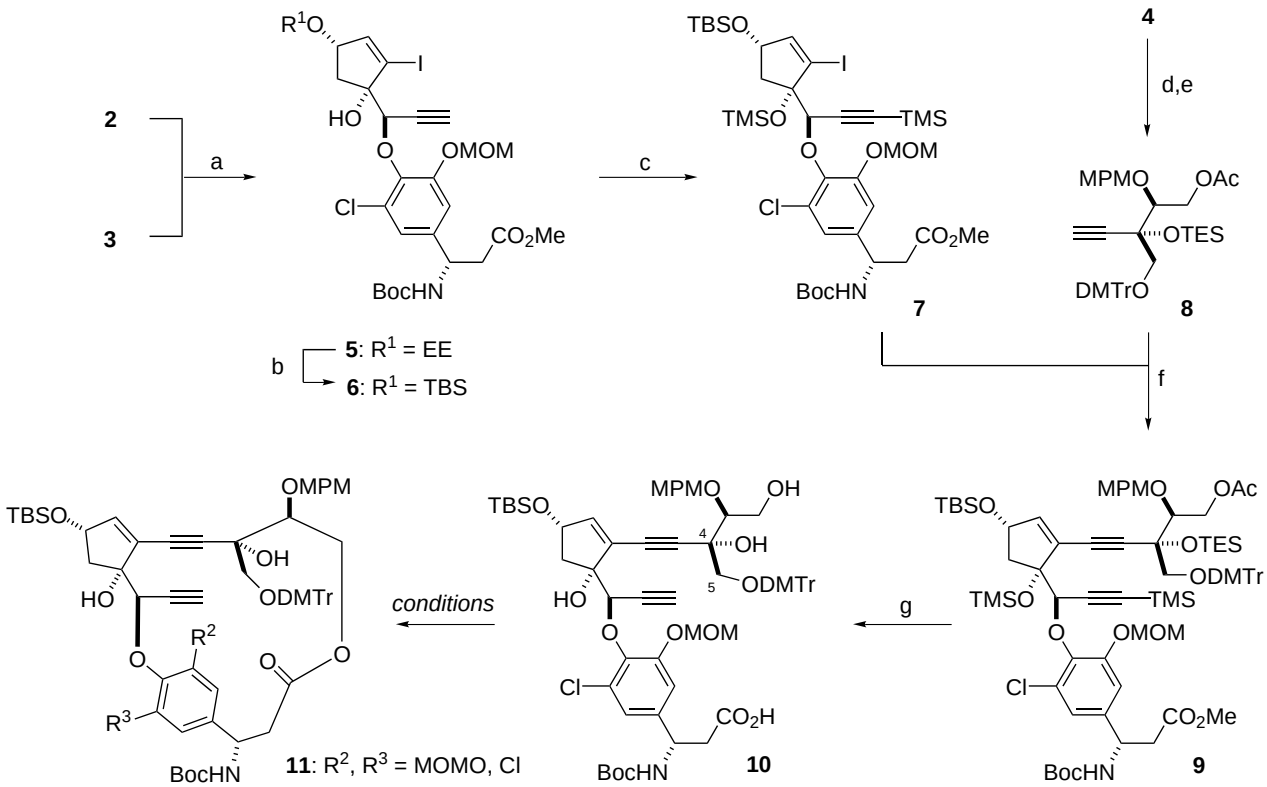
Retrosynthetically, construction of the ansamacrolide moiety of **1** could be attained through the coupling of three fragments (**2**, **3**, **4**, Fig. 1), which in turn could enable formation of the nine-membered ring by linking C5 and C6.[9b] We focused on a macrolactonization approach to build the cyclic structure because of its applicability to complicated systems and tolerance to various functional groups.[12] For this purpose, *seco*-acid **10** was prepared as shown in Scheme 1. CsF-promoted etherification[10,13] between **2** and **3** led to coupling adduct **5** in 61% yield, whose ethoxyethyl group was converted to a TBS group via a two-step sequence to furnish **6**. Stepwise protection of the tertiary alcohol and the acetylene in **6** produced **7** in 74% overall yield in four steps. Compound **8** was obtained in 85% overall yield by acetylation of **4**, followed by treatment with TESOTf in the presence of base. The intermolecular Sonogashira reaction of **7** with **8** afforded adduct **9**. Then, compound **9** was converted to *seco*-acid **10** by sequential alkaline treatment involving: (1) K_2CO_3 in methanol to remove the acetyl, TMS and TES groups; then (2) KOH in H_2O–THF for the saponification.

Results of the macrolactonization of triol **10** are summarized in Scheme 1. Whereas both Mukaiyama[14] (entry 1) and Yamaguchi[15] (entry 2) conditions gave a dimer as the major product, the Corey–Nicolaou procedure[16] allowed selective formation of the desired compound **11** (entry 3). Namely, treatment of carboxylic acid **10** with 2,2′-dipyridyl disulfide in the pres-

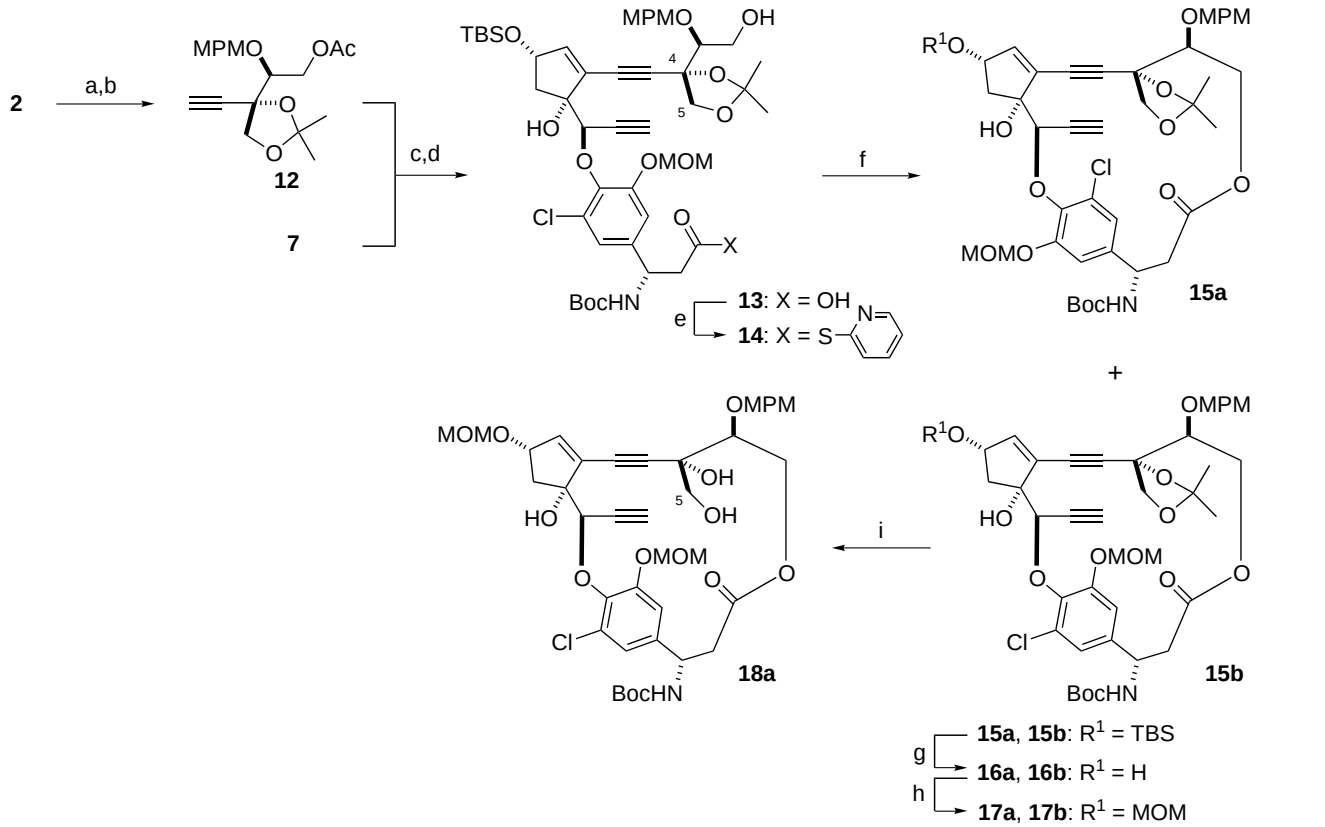


Entry	reagents and conditions	**11**	dimer
1	1-methyl-2-chloro pyridinium iodide Et_3N, CH_3CN (5 mM), 85 °C	6%	26%
2	(i) $(C_6H_2Cl_3)COCl$, Et_3N, toluene, rt (ii) DMAP, toluene (1 mM), rt	14%	41%
3	(i) 2,2'-dipyridyl disulfide, Ph_3P, THF, rt, 81% (ii) toluene (1 mM), 120 °C	29%	—
4	(i) 2,2'-dipyridyl disulfide, Ph_3P, THF, rt, 81% (ii) DMAP, toluene (1 mM), 80 °C	13%	34%

Scheme 1. *Reagents and conditions*: (a) **3** (1.1 equiv.), CsF, DMF, 80°C, 61% (76% based on recovered **2**); (b) (i) PPTS, MeOH; (ii) TBSCl, imidazole, DMF; (c) (i) TMSCl, imidazole, DMF; (ii) $LiN(TMS)_2$, TMSCl, THF, −78°C, 74% (four steps); (d) Ac_2O, pyridine, DMAP, CH_2Cl_2, 91%; (e) TESOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 93%; (f) **8** (1.3 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (30 mol%), CuI (30 mol%), *i*-Pr_2NEt, DMF, 68%; (g) (i) K_2CO_3, MeOH; (ii) KOH, H_2O–MeOH–THF, 59% (two steps).

ence of Ph_3P afforded its corresponding thioester in 81% yield, which was then heated in refluxing toluene to produce **11** as a 1:1.3 mixture of atropisomers in 29% yield. Interestingly, any further activation of the thioester using DMAP[17] resulted in the predominant formation of a dimer (entry 4), suggesting that highly reactive species tend to facilitate an intermolecular reaction instead of an intramolecular pathway for this substrate. The ratio of atropisomers was unaffected by the reaction conditions, presumably due to the similarity of the steric demand between the chloride and MOM-oxy groups on the aromatic ring. Despite the reproducibility of this cyclization protocol, modifying the structure of the *seco*-acid could optimize the yield.

It was reasoned that the low yield of this cyclization step was due to the DMTr group on primary hydroxyl group in **10** projecting toward the β-tyrosine part of the molecule, which would therefore inhibit the efficient formation of the macrocyclic ring.[18] In order to test this hypothesis, we decided to prepare the acetonide derivative **13** (Scheme 2). Compound **2** was selectively protected as the mono-acetate, and following acidic treatment and acetonide formation, yielded compound **12**. Coupling of **12** with iodoolefin **7** under Sonogashira



Scheme 2. *Reagents and conditions*: (a) (i) Ac_2O, pyridine, DMAP, CH_2Cl_2; (ii) PPTS, MeOH, 84% (two steps); (b) 2-methoxypropene, PPTS, DMF, 84%; (c) **12** (1.3 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (20 mol%), CuI (40 mol%), *i*-Pr_2NEt, DMF, 54%; (d) (i) K_2CO_3, MeOH; (ii) KOH, H_2O–MeOH–THF, 76% (two steps); (e) 2,2′-dipyridyl disulfide, PPh_3, THF, 98%; (f) toluene (1 mM), 120°C, dropwise for 6 h, then 6 h, 57%; (g) TBAF, THF; then SiO_2 separation, 40% (**16a**, desired isomer), 44% (**16b**, undesired isomer); (h) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 85% (**17a**), 82% (**17b**); (i) TfOH, CF_3CH_2OH–THF (5:1), 0°C, 73%.

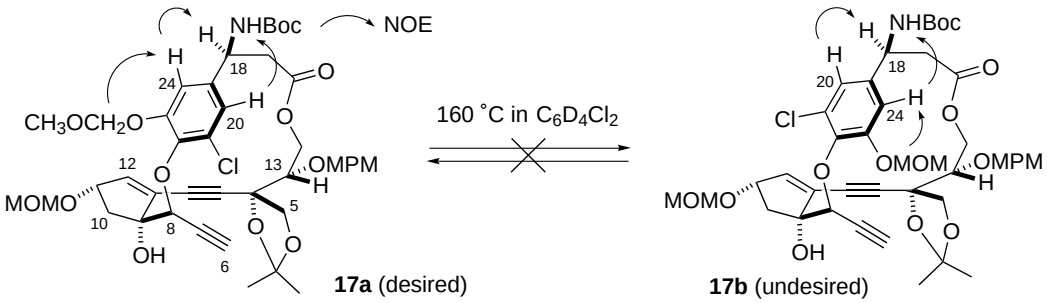


Figure 2. Structure of atropisomers and attempted isomerization experiment.

conditions led to the formation of the adduct in 54% yield, which was converted to carboxylic acid **13** via a two-step sequence in 76% overall yield.

As expected, the Corey–Nicolaou macrolactonization of **13** did give a better yield than that of **10**. Thioester **14** was prepared in 98% yield by the action of 2,2′-dipyridyl disulfide and PPh_3. By heating **14** to reflux in toluene, the macrolactone was isolated in 57% yield as an inseparable 1:1.1 mixture of atropisomers **15a** and **15b**, respectively. These isomers were separated by SiO_2 chromatography after TBS ether deprotection. Compounds **16a** and **16b** were then separately converted to their methoxymethyl ethers (**17a**, **17b**), whose stereostructures were determined unambiguously by NOESY experiments (Fig. 2).[19]

To investigate the thermodynamic behavior of each atropisomer, **17a** and **17b** were separately heated to 160°C in deuterated 1,2-dichlorobenzene for 12 h (Fig. 2).[20] However, no isomerization was observed under these conditions and the substrates slowly decomposed. Thus, the problem of controlling the atropisomer remains to be solved.

Lastly, it was necessary to liberate the C5 hydroxy group for further synthetic manipulation. After extensive experimentation, selective removal of the acetonide group was achieved by treating **17a** with trifluoromethanesulfonic acid in trifluoroethanol at 0°C.[21] In this way, triol **18a** was generated in 73% yield and anticipated to be a key intermediate for the total synthesis of the C-1027 chromophore.

In conclusion, we have developed an efficient strategy for the construction of macrolactones by screening both the reaction conditions and the substrates. The acetonide group proved to be the superior protective group for efficient cyclization of this system. Further studies for the total synthesis of C-1027 chromophore, including that of the formation of the nine-membered ring, are currently underway in this laboratory.

References

1. Zhen, Y.-s.; Ming, S.-y.; Bin, Y.; Otani, T.; Saito, H.; Yamada, Y. *J. Antibiot*. **1989**, *42*, 1294.
2. Otani, T.; Minami, Y.; Marunaka, T.; Zhang, R.; Xie, M.-Y. *J. Antibiot*. **1988**, *41*, 1580.
3. For recent reviews on chromoprotein antibiotics and other enediyne natural products, see: (a) *Neocarzinostatin*; Maeda, H.; Edo, K.; Ishida, N., Eds.; Springer: Tokyo, 1997; (b) Xi, Z.; Goldberg, I. H. In *Comprehensive Natural Products Chemistry*; Barton, D. H. R.; Nakanishi, K., Eds.; Elsevier, 1999; Vol. 7, p. 553.
4. (a) Minami, Y.; Yoshida, K.-i.; Azuma, R.; Saeki, M.; Otani, T. *Tetrahedron Lett*. **1993**, *34*, 2633; (b) Yoshida, K.-i.; Minami, Y.; Azuma, R.; Saeki, M.; Otani, T. *Tetrahedron Lett*. **1993**, *34*, 2637; (c) Iida, K.; Ishii, T.; Hirama, M.; Otani, T.; Minami, Y.; Yoshida, K.-i. *Tetrahedron Lett*. **1993**, *34*, 4079; (d) Iida, K.-i.; Fukuda, S.; Tanaka, T.; Hirama, M.; Imajo, S.; Ishiguro, M.; Yoshida, K.-i.; Otani, T. *Tetrahedron Lett*. **1996**, *38*, 4997.
5. Xu, Y.-j.; Zhen, X.; Zhen, Y.-s.; Goldberg, I. H. *Biochemistry* **1997**, *36*, 14975 and references cited therein.
6. (a) Iida, K.-i.; Hirama, M. *J. Am. Chem. Soc*. **1995**, *117*, 8875; (b) Hirama, M. *Pure Appl. Chem*. **1997**, *69*, 525.
7. (a) Hirama, M.; Akiyama, K.; Tanaka, T.; Noda, T.; Iida, K.-i.; Sato, I.; Hanaishi, R.; Otani, T.; Leet, J. E. *J. Am. Chem. Soc*. **2000**, *122*, 720; (b) Tanaka, T.; Fukuda-Ishisaka, S.; Hirama, M.; Otani, T. *J. Mol. Biol*. **2001**, *309*, 267.
8. For recent synthetic studies on nine-membered enediyne antibiotics, see: (a) Myers, A. G.; Liang, J.; Hammond, M.; Harrington, P. M.; Wu, Y.; Kuo, E, Y. *J. Am. Chem. Soc*. **1998**, *120*, 5319; (b) Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed*. **2000**, *39*, 2732; (c) Magnus, P.; Carter, R.; Davies, M.; Elliott, J.; Pitterna, T. *Tetrahedron* **1996**, *52*, 6283; (d) Caddick, S.; Delisser, V. M.; Doyle, V. E.; Khan, S.; Avent, A. G.; Vile, S. *Tetrahedron* **1999**, *55*, 2737; (e) Tanaka, H.; Yamada, H.; Matsuda, A.; Takahashi, T. *Synlett* **1997**, 381 and references cited therein.
9. (a) Iida, K.-i.; Hirama, M. *J. Am. Chem. Soc*. **1994**, *116*, 10310; (b) Sato, I.; Toyama, K.; Kikuchi, T.; Hirama, M. *Synlett* **1998**, 1308.
10. Sato, I.; Kikuchi, T.; Hirama, M. *Chem. Lett*. **1999**, 511.
11. Sato, I.; Akahori, Y.; Sasaki, T.; Kikuchi, T.; Hirama, M. *Chem. Lett*. **1999**, 867.
12. Although other cyclization strategies, such as intramolecular Sonogashira coupling or intramolecular epoxide opening reaction, were pursued, we could not improve the yield above 25%. These results will be discussed in a full account.
13. Kawata, S.; Hirama, M. *Tetrahedron Lett*. **1998**, *39*, 8707.
14. Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett*. **1976**, 49.
15. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989.
16. Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc*. **1974**, *96*, 5614.
17. Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem*. **1990**, *55*, 7.
18. We applied a similar protective group strategy for the intramolecular Sonogashira coupling in a synthetic study of kedarcidin chromophore, see: Yoshimura, F.; Kawata, S.; Hirama, M. *Tetrahedron Lett*. **1999**, *40*, 8281.
19. Physical data for **17a** and **17b**. **17a**: IR (film) 3468, 3283, 2927, 2122, 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.24 (2H, d, $J=8.5$ Hz, Ar), 6.96 (1H, s, H20), 6.95 (1H, s, H24), 6.86 (2H, d, $J=8.5$ Hz, Ar), 6.24 (1H, d, $J=2.5$ Hz, H12), 5.41 (1H, brs, N*H*), 5.22 (1H, d, $J=6.0$ Hz, CH_3OCH_2), 5.09 (1H, d, $J=6.0$ Hz, CH_3OCH_2), 5.20 (1H, br, H18), 4.82 (1H, brs, H8), 4.75 (1H, ddd, $J=7.5$, 5.5, 2.5 Hz, H11), 4.73 (1H, d, $J=7.0$ Hz, CH_3OCH_2), 4.70 (1H, d, $J=7.0$ Hz, CH_3OCH_2), 4.57 (1H, d, $J=11.5$ Hz, $ArCH_2$), 4.41 (1H, d, $J=11.5$ Hz, $ArCH_2$), 4.02 (1H, d, $J=8.5$ Hz, H5), 4.00 (1H, m, H14), 3.89 (1H, br, H13), 3.89 (1H, brd, $J=8.5$ Hz, H5), 3.81 (3H, s, CH_3OAr), 3.78 (1H, s, O*H*), 3.49 (3H, s, CH_3OCH_2), 3.40 (3H, s, CH_3OCH_2), 3.19 (1H, dd, $J=13.5$, 7.5 Hz, H10), 3.06 (1H, br, H14), 2.94 (1H, br, H17), 2.61 (1H, d, $J=2.5$

Hz, H6), 2.40 (1H, br, H17) 1.94 (1H, dd, $J=13.5$, 5.5 Hz, H10), 1.45 (3H, s, CH_3), 1.45 (9H, s, $(CH_3)_3C$), 1.37 (3H, s, CH_3); MALDI-TOF MS calcd for $C_{43}H_{52}O_{14}ClNNa$ $[M+Na]^+$ 864.3, found 864.2. **17b**: IR (film) 3468, 3282, 2925, 2122, 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29 (2H, d, $J=8.5$ Hz, Ar), 7.01 (1H, s, H24), 6.95 (1H, s, H20), 6.88 (2H, d, $J=8.5$ Hz, Ar), 6.23 (1H, d, $J=2.0$ Hz, H12), 5.57 (1H, bs, N*H*), 5.25 (1H, s, O*H*), 5.22 (1H, d, $J=6.5$ Hz, CH_3OCH_2), 5.15 (1H, d, $J=6.5$ Hz, CH_3OCH_2), 5.08 (1H, s, H18), 4.78 (1H, ddd, $J=7.5$, 5.5, 2.0 Hz, H11), 4.73 (1H, d, $J=7.0$ Hz, CH_3OCH_2), 4.72 (1H, br, $ArCH_2$), 4.69 (1H, d, $J=7.0$ Hz, CH_3OCH_2), 4.63 (1H, brs, H8), 4.63 (1H, br, $ArCH_2$), 4.02 (1H, d, $J=9.0$ Hz, H5), 3.82 (3H, s, CH_3OAr), 3.81 (1H, d, $J=9.0$ Hz, H5), 3.75 (1H, m, H13), 3.50 (3H, s, CH_3OCH_2), 3.40 (3H, s, CH_3OCH_2), 3.35 (2H, m, H14), 3.30 (1H, dd, $J=14.0$, 7.5 Hz, H10), 2.82 (1H, dd, $J=13.0$, 6.0 Hz, H17), 2.65 (1H, d, $J=1.5$ Hz, H6), 2.46 (1H, br, H17), 1.87 (1H, dd, $J=14.0$, 5.5 Hz, H10), 1.50 (3H, s, CH_3), 1.46 (9H, s, $(CH_3)_3C$), 1.35 (3H, s, CH_3); MALDI-TOF MS calcd for $C_{43}H_{52}O_{14}ClNNa$ $[M+Na]^+$ 864.3, found 864.2.

20. For an excellent example of the selective isomerization of atropisomers in the context of a total synthesis of vancomycin, see: Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004.
21. (a) Kobayashi, S.; Reddy, R. S.; Sugiura, Y.; Sasaki, D.; Miyagawa, N.; Hirama, M. *J. Am. Chem. Soc.* **2001**, *123*, 2887; (b) Halcombe, J. L.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 111.