JOC Article

Studies on the Total Synthesis of Streptazolin and Its Related Natural Products: First Total Synthesis of (±)-8α-Hydroxystreptazolone

Izumi Nomura and Chisato Mukai*

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi 13-1, Kanazawa 920-0934, Japan

cmukai@kenroku.kanazawa-u.ac.jp

Received November 15, 2003

The intramolecular Pauson−Khand reaction of 2-oxazolone derivatives with a suitable heptynyl appendage gave exclusively the corresponding 4-hydroxy-6-substituted-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]-undec-5-ene-7,10-diones. On the basis of this newly developed Pauson−Khand reaction of 2-oxazolone-alkyne derivatives, the first total synthesis of (±)-8α-hydroxystreptazolone was accomplished in a highly stereoselective manner. In addition, (±)-7-*epi*-8α-hydroxystreptazolone was also synthesized.

Introduction

Streptazolin (**1**) was first isolated from a culture of *Streptomyces viridochromogenes* by Drautz et al. in 1981.[1] This lipophilic neutral tricyclic compound has been shown to possess antibiotic and antifungal activities.[2] Tang et al.[3] recently reported the isolation of some of the novel and more oxidized streptazolin-related natural products, 8α-hydroxystreptazolone (**2**),[4] 4,12-epoxystreptazoline (**3**),[4] and 9*β*-hydroxystreptazoline (**4**).[4] In addition to these, the streptazolin dimer (**5**)[4] together with streptazolin (**1**) and related known compounds[5] as secondary metabolites from *Streptomyces* sp. and *S. viridochromogenes* were isolated, all via chemical screening. Because of its unique structural features as well as its promising biological activity profile, the first-isolated streptazolin (**1**), having the common basic skeleton of the streptazolin analogues, has been synthesized by four groups.[6−9] The total synthesis of **1** was first reported by Kozikowski and Park[6] in racemic form through the intramolecular nitrile oxide [2 + 3]-cycloaddition for construction of the azabicyclo[4.3.0] framework. Overman and Flann[7] completed the first enantioselective synthesis of **1** starting from L-tartrate via a ring-closing reaction between the *N*-acyliminium cation and the vinylsilane species for construction of the azabicyclo[4.3.0] framework. Kibayashi and co-workers[8] also reported an enantioselective synthesis of **1** starting from L-tartrate by taking advantage of a palladium-mediated ring-closure reaction. Comins and Huang[9] recently revealed an asymmetric synthesis of **1** based on a chiral auxiliary-mediated asymmetric preparation of the dihydropyridone derivative, followed by palladium-mediated construction of the tricyclic framework. All these syntheses of streptazolin (**1**) used a stepwise procedure for the construction of the 9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undecan-10-one skeleton (Figure 1).

As part of our study on the total synthesis of natural products based on the Pauson−Khand reaction,[10] we have devoted considerable attention to the total synthesis of streptazolin and its related natural products. A general retrosynthetic analysis for streptazolin and its analogues is outlined in Scheme 1. A common structural feature of these natural products[1−3,5−9,11] is the 7-hydroxy-6-substituted-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undecan-10-one framework **6**.[4] Therefore, we envisioned the tricyclic core framework, namely 4-hydroxy-6-(C_2-unit)-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-ene-7,10-dione **7**,[4] being the key intermediate for further elaboration leading to the

* To whom correspondence should be addressed. Tel: +81-76-234-4411. Fax: +81-76-234-4410.

(1) Drautz, H,; Zähner, H.; Kupfer, E.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981**, *64*, 1752.

(2) (a) Grabley, S.; Kluge, H.; Hoppe, H.-U. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 664. (b) Grabley, S.; Hammann, P.; Kluge, H.; Wink, J.; Kricke, P.; Zeeck, A. *J. Antibiot.* **1991**, *44*, 797. (c) Grabley, S.; Hammann, P.; Thiericke, R.; Wink, J.; Philipps, S.; Zeeck, A. *J. Antibiot.* **1993**, *46*, 343.

(3) Tang, Y.-Q.; Wunderlich, D.; Sattler, I.; Grabley, S.; Feng, X.-Z.; Thiericke, R. Abstract of Division of Organic Chemistry. *223rd ACS National Meeting*, Apr 7−12, Orlando; American Chemical Society: Washington, DC, 2002; p 341.

(4) Tang et al. called compound **2** 8α-hydroxystreptazolone, compound **3** 4,12-epoxystreptazolin, compound **4** 9*β*-hydroxystreptazolin, and compound **5** streptazolin dimer.[3] According to the IUPAC nomenclature system, (±)-**2** should be described as (4*R**,7*R**,8*R**,11*R**)-6-acetyl-4,7-dihydroxy-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-en-10-one. This numbering system is used for the tricyclic compounds in this manuscript.

(5) Puder, C.; Loya, S.; Hizi, A.; Zeeck, A. *J. Nat. Prod.* **2001**, *64*, 42.

(6) (a) Kozikowski, A. P.; Park, P. *J. Am. Chem. Soc.* **1985**, *107*, 1763. (b) Kozikowski, A. P.; Park, P. *J. Org. Chem.* **1990**, *55*, 4668.

(7) Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6115.

(8) Yamada, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **1996**, *118*, 1054.

(9) Huang, S.; Comins, D. L. *J. Chem. Soc., Chem. Commun.* **2000**, 569.

(10) Mukai, C.; Kobayashi, M.; Kim, I. J.; Hanaoka, M. *Tetrahedron* **2002**, *58*, 5225.

(11) (a) Cossy, J.; Pévet, I.; Meyer, C. *Synlett* **2000**, 122. (b) Cossy, J.; Pévet, I.; Meyer, C. *Eur. J. Org. Chem.* **2001**, 2841.

10.1021/jo0356816 CCC: $27.50
Published on Web 01/21/2004

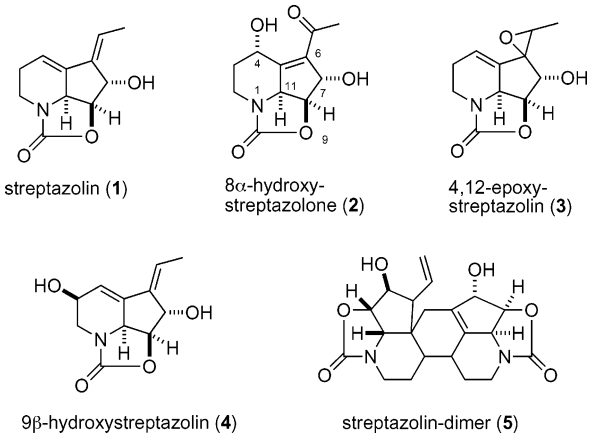
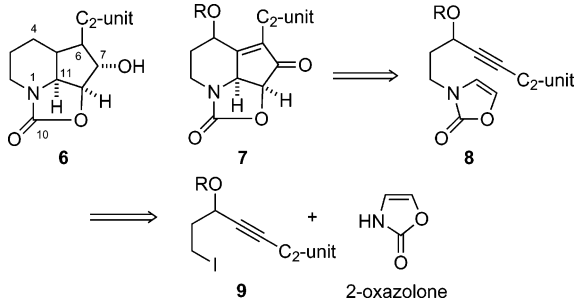


FIGURE 1. Streptazolin and its related natural products.

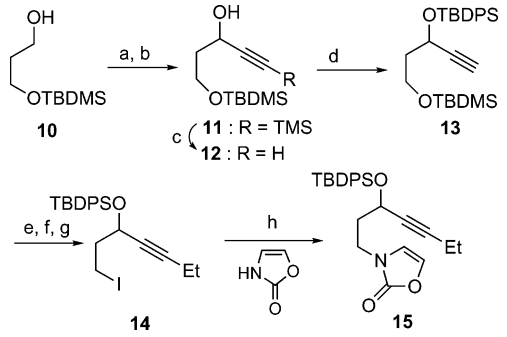
SCHEME 1



synthesis of various streptazolin-related natural products. The tricyclic skeleton **7** might be directly constructed by the intramolecular Pauson−Khand reaction of the 2-oxazolone derivative **8** which has a suitable heptynyl moiety on the nitrogen atom. To the best of our knowledge, no previous reports have dealt with 2-oxazolone derivatives as the olefin counterpart in the Pauson−Khand reaction. Thus, this would be the first example in which a 2-oxazolone was used as the olefin moiety (an enamine equivalent[12]) in the Pauson−Khand reaction. During these ongoing studies, Magnus[12a] and Pérez-Castells[12b] independently reported examples of the Pauson-Khand reaction of an enamine equivalent. The 2-oxazolone−alkyne derivative **8**, a substrate for the Pauson−Khand reaction, can be prepared from the coupling reaction between the heptynyl iodo derivative **9** and 2-oxazolone.

On the basis of the above simple retrosynthetic analysis, (±)-8α-hydroxystreptazolone (**2**)[3,4] was chosen as our first target natural product in this investigation. In this paper, we describe in detail the results[13] relating (i) the development of the stereoselective and direct construction of the 9-oxa-1-azatricyclo[6.2.1.$0^{5,11}$]undec-5-ene-7,10-dione skeleton (e.g., **7**) via the intramolecular Pauson−Khand reaction of 2-oxazolone derivatives and (ii) its successful application to the first total synthesis of (±)-8α-hydroxystreptazolone (**2**).

SCHEME 2[a]



[a] Reaction conditions: (a) SO_3·Py, DMSO, Et_3N, CH_2Cl_2, 0°C; (b) ^{n}BuLi, TMSC≡CH, THF, −78°C (75%); (c) K_2CO_3, MeOH, rt (97%); (d) TBDPSCl, imid, DMF, rt, (98%); (e) ^{n}BuLi, THF, −35°C, then EtI, 45°C; (f) PPTS, MeOH, rt; (g) I_2, PPh_3, imid, CH_2Cl_2, rt (69%); (h) 2-oxazolone, NaH, DMF, 0°C (86%).

Results and Discussion

Intramolecular Pauson−Khand Reaction of 2-Oxazolone Derivatives. Since the targeted streptazolin-related natural products have a C_2-unit at the C_6-position,[4] we first prepared the 2-oxazolone−alkyne derivative **15** with the simplest C_2-unit, an ethyl group, at the triple bond terminus to not only identify suitable ring-closing conditions, but also to determine the level of stereoselectivity that could be expected in the intramolecular Pauson−Khand reaction. Thus, the 2-oxazolone−alkyne derivative **15**, required for the intramolecular Pauson−Khand reaction of our retrosynthesis, was easily prepared from the known alcohol **10** by conventional means, as shown in Scheme 2. Oxidation of **10** was followed by addition of the acetylide derived from trimethylsilylacetylene to afford **11** in 75% yield. The terminal silyl group of **11** was removed by base treatment to afford **12**,[14] the secondary hydroxyl group of which was protected with a *tert*-butyldiphenylsilyl (TBDPS) group to give **13** in 98% yield. Introduction of an ethyl group at the triple bond terminus of **13** was followed by desilylation and iodination to furnish the iodo derivative **14** in 69% overall yield. The coupling reaction between **14** and 2-oxazolone proceeded, upon treatment with NaH in DMF, to produce **15** in 86% yield.

We began the intramolecular Pauson−Khand reaction of the 2-oxazolone derivative by treating **15** with $Co_2(CO)_8$ in Et_2O at room temperature to give the corresponding cobalt complex, which was heated in acetonitrile[15] without a promoter to give only a trace amount of **16**. When the cobalt complex was exposed to trimethylamine *N*-oxide dihydrate (TMANO·$2H_2O$, 3.5 equiv)[16] in THF at room temperature for 3 h, the desired tricyclic compound **16** was obtained in 37% yield as the sole isolable product (Scheme 3). The relative stereochemistry of **16** was determined by ^{1}H NMR spectral considerations. Compound **16** was converted into the acetate derivative **17**

(12) Very recently, the carbamate and amide functionalities were used as enamine equivalents in the Pauson−Khand reaction. (a) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947. (b) Domínguez, G.; Casarrubios, L.; Rodríguez-Noriega, J.; Pérez-Castells, J. *Helv. Chim. Acta* **2002**, *85*, 2856.

(13) Part of this work was published as a preliminary communication: Nomura, I.; Mukai, C. *Org. Lett.* **2002**, *4*, 4301.

(14) (a) Takano, S.; Sugihara, T.; Ogasawara, K. *Tetrahedron Lett.* **1991**, *32*, 2797. (b) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1994**, *59*, 5662.

(15) (a) Hoye, T. R.; Suriano, J. A. *J. Org. Chem.* **1993**, *58*, 1659. (b) Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220.

(16) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204.

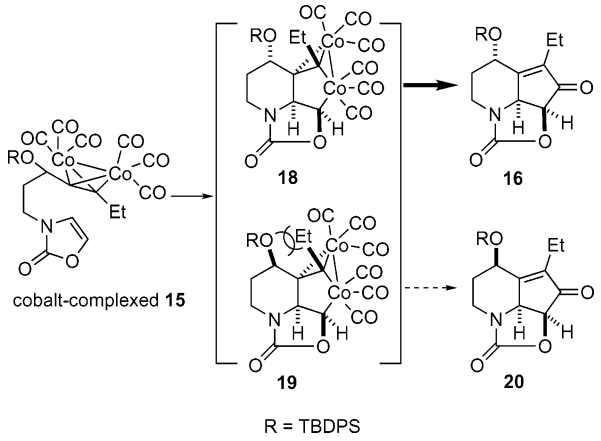
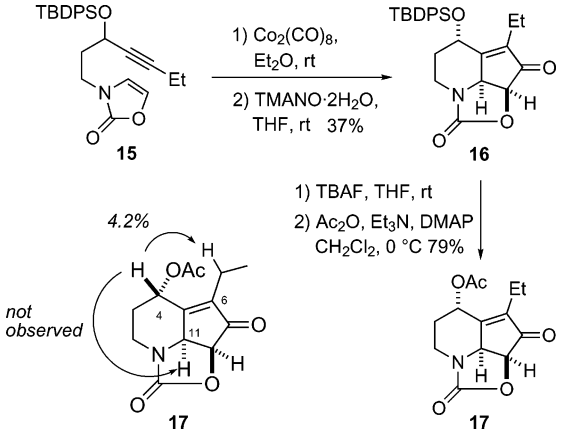


FIGURE 2. Proposed mechanism for Pauson−Khand reaction.

SCHEME 3

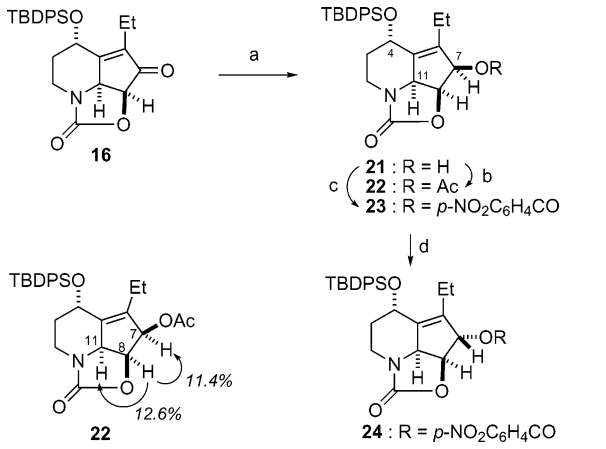


in 79% yield by treatment with tetra-*n*-butylammonium fluoride (TBAF) and then acetic anhydride. The NOE study of **17** showed no enhancement between H-4 and H-11, whereas the methylene protons of the C_6-ethyl group were enhanced by 4.2% upon irradiation at H-4. This observation was in good accord with the prediction based on analysis of the molecular model.

Although the chemical yield (37%) of **16** was not satisfactory, we could synthesize stereoselectively the desired tricyclic product **16**, having the core common framework of the target natural products, from the 2-oxazolone−alkyne derivative **15** in a straightforward manner. The mechanism for the stereoselective formation of **16** is uncertain, but it might be tentatively rationalized on the basis of the mechanistic hypothesis proposed by Magnus (Figure 2).[17] Two plausible cobalt−metallocyclic intermediates **18** and **19**, derived from the cobalt-complexed **15**, would collapse to the desired **16** and its C_4-epimer **20**. In the cobalt−metallocycle **19** leading to **20**, the bulky siloxy group at the C_4-position would have a nonbonding interaction with the C_2-carbon appendage (ethyl group) at the triple bond terminus due to a kind of 1,3-pseudodiaxial relationship on the sterically congested concave face of the transient cobaltabicyclic structure; therefore, a serious unfavorable interaction could occur. This would not be the case in the intermediate **18** where the siloxy group and the C_2-substituent (ethyl group) have a trans alignment. As a result, the cyclization pathway via the intermediate **18** would be preferred over that via **19**.

(17) (a) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851. (b) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861.

SCHEME 4[a]

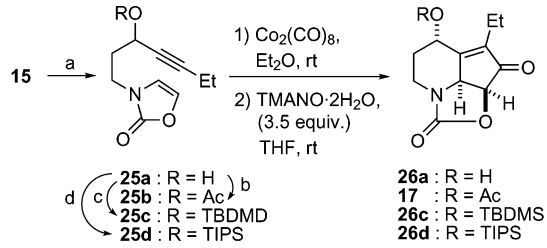


[a] Reaction conditions: (a) $NaBH_4$, $CeCl_3$, MeOH, 0 °C (quant); (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (99% from **16**); (c) *p*-$NO_2C_6H_4COCl$, Et_3N, DMAP, CH_2Cl_2, 40 °C (95% from **16**); (d) *p*-$NO_2C_6H_4CO_2H$, DEAD, PPh_3, benzene, rt (94% from **16**).

We next sought to transform the carbonyl functionality of the tricyclic compound **16** into a hydroxyl group with the same relative stereochemistry as that of the target natural products (Scheme 4). Thus, reduction of **16** with $NaBH_4$ in the presence of $CeCl_3$ gave the alcohol **21** in a quantitative yield, which was then acetylated under conventional conditions to provide **22** in 99% yield. In the NOE study of **22**, irradiation of H-8 produced a 11.4% enhancement of H-7 as well as a 12.6% enhancement of H-11, clearly showing that the newly generated stereogenic center (C_7-position) was not the same as that of streptazolin (**1**) and its related natural products. Inversion of the configuration at the C_7-position was realized by exposure of **21** to Mitsunobu conditions (*p*-nitrobenzoic acid, diethyl azodicarboxylate (DEAD), and triphenylphosphine), which led to the exclusive formation of **24** with the inverted stereochemistry at the C_7-position in 96% yield. H-7 of **24** appeared at δ 5.80 as a singlet in its ^{1}H NMR spectrum, while the ^{1}H NMR spectrum of the corresponding *p*-nitrobenzoate derivative **23**, derived from **21** by acylation, revealed H-7 at δ 5.89 as a doublet (J = 4.9 Hz). It has been shown that H-7 of streptazolin (**1**) and its acetate resonate as singlets in their ^{1}H NMR spectra.[1,8] Thus, comparison of the coupling constant between H-7 and H-8 in both **23** and **24** with those of the related natural products, in combination with the results of the NOE experiments of **22**, unambiguously established that both **23** and **24** have the stereochemistries depicted in Scheme 4.

We could now develop a procedure for constructing the tricyclic framework of streptazolin and its related natural products, in which all of the stereogenic centers of 8α-hydroxystreptazolone (**2**) are constructed in a stereocontrolled fashion. Prior to turning our efforts to the total synthesis of the target natural product, the most significant issue remaining to be solved at this point was to optimize the ring-closing conditions for the conversion of

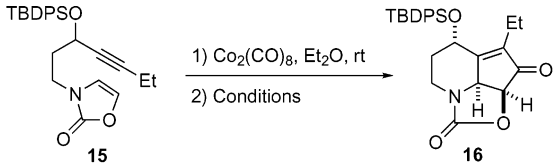
TABLE 1. Pauson−Khand Reaction of 2-Oxazolone Derivative 25[a]



entry	substrate	R	time	product	yield (%)
1	**25a**	H	6 h	**26a**	20
2	**25b**	Ac	20 h	**17**	14
3	**25c**	TBDMS	1 h	**26c**	14
4	**25d**	TIPS	1.5 h	**26d**	29

[a] Reaction conditions: (a) TBAF, THF, rt (98%); (b) Ac_2O, CH_2Cl_2, rt (94% from **15**); (c) TBDMSCl, imid, DMF, 50 °C (86% from **15**); (d) TIPSCl, imid, DMF, 50°C (85% from **15**).

TABLE 2. Pauson−Khand Reaction of 2-Oxazolone Derivative 15



entry	promoter	equiv.	solvent	temp.	time	yield (%)
1	TMANO·$2H_2O$	3.5	THF	reflux	3.5 h	23
2	TMANO·$2H_2O$	4.5	CH_2Cl_2	reflux	5.5 h	55
3	NMO	4.5	CH_2Cl_2	rt	20 h	38
4	^{i}PrSMe	3.5	$ClCH_2CH_2Cl$	reflux	45 min	16
5	^{n}BuSMe	3.5	$ClCH_2CH_2Cl$	reflux	1 h	14
6	Cyclohexylamine	3.5	$ClCH_2CH_2Cl$	reflux	30 min	11
7	TMANO/4Å MS	4.5	toluene	-10 °C	12 h	60

the 2-oxazolone derivative **15** into the tricyclic compound **16**. The first effort was directed toward determining the influence of the protecting group on the secondary hydroxyl group at the propargyl position in the Pauson-Khand reaction. Compound **15** was desilylated with TBAF to give the hydroxyl derivative **25a** (98%), which was subsequently protected with three different protecting groups to afford **25b**, **25c**, and **25d**, respectively. With four newly synthesized precursors for the Pauson−Khand reaction in hand, we next investigated the ring-closing reaction of these compounds under the conditions described for the preparation of **16** (Scheme 3). The results are summarized in Table 1. The hydroxyl derivative **25a** and the TIPS-protected compound **25c** provided the corresponding cyclized products in 20% and 29% yields, respectively (entries 1 and 4). However, both yields were lower than that of **16** (37%). Thus, no improvement was achieved by changing the protecting group on the hydroxyl functionality. On the basis of the observation in Table 1 and the result of the reaction of **15**, it might be concluded that a bulky protection group would be favorable in this transformation. Interestingly, it took somewhat longer (20 h) to consume the starting material when the acetyl congener **25b** was submitted to the standard conditions, presumably due to the electron-withdrawing nature of the acetoxy group at the propargyl position (entry 2).

We next screened various Pauson−Khand conditions by using compound **15**. Table 2 summarizes several typical results. The Pauson−Khand reaction of **15** with TMANO·$2H_2O$ (3.5 equiv)[16] in refluxing CH_2Cl_2 instead of THF at room temperature gave a lower yield (23%, entry 1). Increasing of the amount of TMANO·$2H_2O$ to 4.5 equiv in refluxing CH_2Cl_2 afforded **16** in an improved yield of 55% (entry 2). Another *N*-oxide promoter, *N*-methylmorpholine *N*-oxide (NMO)[18] in CH_2Cl_2 at room temperature, produced **16** in 38% yield (entry 3), similar to that obtained with TMANO·$2H_2O$ in THF. Sugihara's method[19] of using amines or sulfides as the promoter did not improve the yield of **16** (entries 4 to 6). However, the procedure developed by Pérez-Castells[20] was found to be effective for our purposes. Thus, the cobalt-complexed 2-oxazolone derivative**15** was exposed to anhydrous TMANO (4.5 equiv) and 4 Å molecular sieves in toluene at −10 °C for 12 h to furnish **16** in 60% yield (entry 7). This transformation was reproducible, and **16** was consistently obtained in the designated yield. We have developed an efficient method for the construction of 4-hydroxy-6-(C_2-unit)-9-oxa-1-azatricyclo[6.2.1.$0^{5,11}$]undec-5-ene-7,10-dione (e.g., **7** in Scheme 1), a possible common synthetic intermediate for streptazolin and its related natural products, in a highly stereoselective manner based on the intramolecular Pauson−Khand reaction of the 2-oxazolone derivative in acceptable yields.

Total Synthesis of (±)-8α-Hydroxystreptazolone. As shown in Figure 1, the target natural product, 8α-hydroxystreptazolone (**2**), has an acetyl group at the C_6-position.[4] Therefore, the 2-oxazolone derivative **29** possessing a vinyl group at the triple bond terminus was chosen as the starting material[21] because a vinyl group is well-known to be easily converted to an acetyl group under the Wacker oxidation conditions (Scheme 5).[22] The 2-oxazolone−enyne derivative **29** was prepared from **13** via **27**and **28** by conventional means. Exposure of **29** to ring-closing condition, optimized in Table 2 (entry 7),[20]

(18) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289.

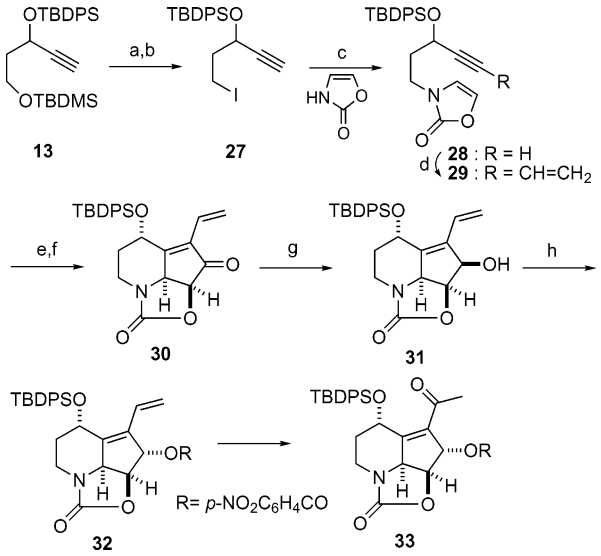
(19) Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2801. (b) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771.

(20) Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Org. Lett.* **1999**, *1*, 1187.

(21) The Pauson−Khand reaction of the 2-oxazolone−alkyne derivative, possessing an acetyl group at the triple bond terminus was not investigated, because it appeared difficult to differentiate the resulting two carbonyl functionalities (the C_6-acetyl group and the C_7-carbonyl moiety) of the tricyclic compound.

(22) For example, see: (a) Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem.* **1962**, *74*, 93. (b) Tsuji, J. *Synthesis*, **1984**, 369−384. (c) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830, and references therein.

SCHEME 5[a]

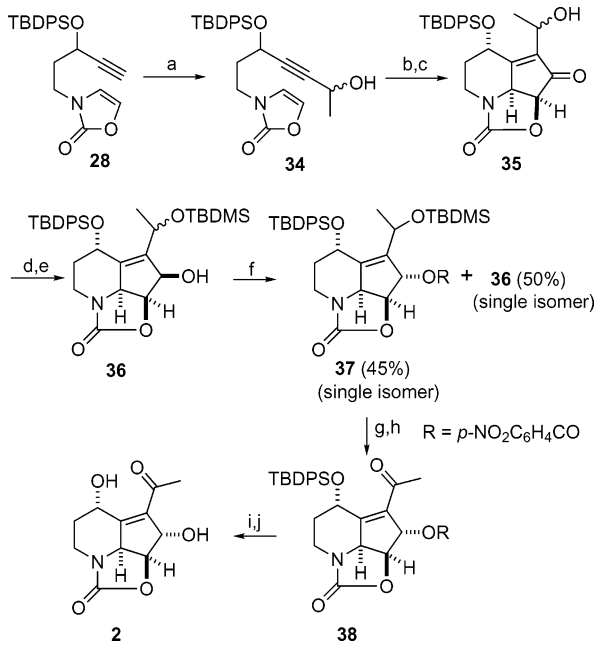


[a] Reaction conditions: (a) PPTS, MeOH, rt; (b) I_2, PPh_3, imid, CH_2Cl_2, rt (99%); (c) 2-oxazolone, NaH, DMF, 0 °C (83%); (d) vinyl bromide, $PdCl_2(PPh_3)_2$, CuI, $^iPr_2NH$, THF, rt (87%); (e) $Co_2(CO)_8$, Et_2O, rt; (f) TMANO, 4 Å MS, toluene, −10 °C (50%); (g) $NaBH_4$, $CeCl_3$, MeOH, 0 °C (quant); (h) *p*-$NO_2C_6H_4CO_2H$, DEAD, PPh_3, benzene, rt (93%).

produced the desired tricyclic compound **30** in 50% yield in a highly stereoselective manner. According to the procedure described for the transformation of **16** to **24**, compound **32** was obtained in high yield from the keto derivative **30** by stereoselective reduction followed by the Mitsunobu reaction. However, it soon became apparent that **32** could not provide the acetyl derivative **33** having all the required functionalities for the synthesis of **2** under the Wacker conditions, but gave instead an intractable mixture.[22] A careful inspection of the ^1H NMR spectrum of the crude mixture disclosed the following observations: (i) disappearance of vinyl protons, (ii) no peaks due to the acetyl group, and (iii) lower field-shifted proton presumably due to an aldehyde functionality. Judging from this observation, we tentatively concluded that oxidative carbon−carbon bond cleavage of the vinyl group must have occurred, although no pure compounds could be isolated from the reaction mixture.

We next addressed the introduction of the 1-hydroxyethyl group as an acetyl precursor at the triple bond terminus of the 2-oxazolone derivative.[21] Treatment of **28** with acetaldehyde in the presence of sodium hexamethyldisilazide (NaHMDS) afforded **34** in 83% yield as a mixture of two diastereoisomers, which were exposed to $Co_2(CO)_8$ under the Pauson−Khand conditions to produce the corresponding tricyclic compound **35** in 51% yield (Scheme 6). Protection of the secondary hydroxyl moiety of **35** with the TBDMS group was followed by stereoselective reduction of the carbonyl functionality to furnish **36** in 78% yield. According to our model studies (transformation of **21** to **24** in Scheme 4), inversion of the C_7-hydroxyl group of **36** (a mixture of two diastereoisomers) was carried out under Mitsunobu conditions at room temperature to give the inverted product **37** in 45% yield along with 50% yield of the recovered starting material **36**. Complete consumption of the starting material **36** could not be achieved even at higher reaction

SCHEME 6[a]

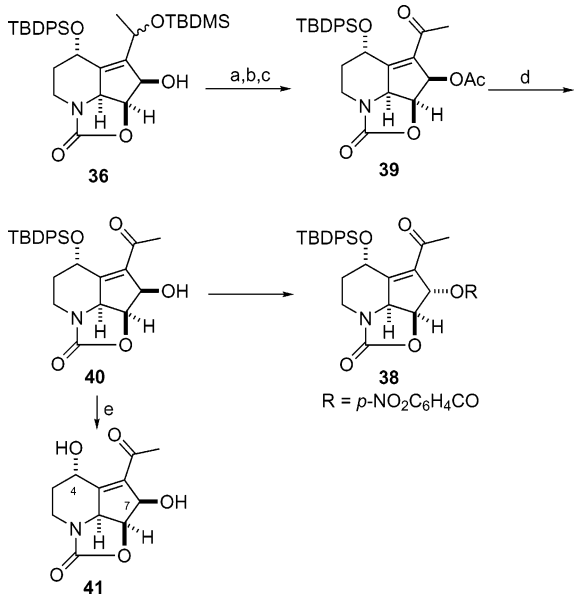


[a] Reaction conditions: (a) NaHMDS, CH_3CHO, THF, −78 °C (83%); (b) $Co_2(CO)_8$, Et_2O, rt; (c) TMANO, 4 Å MS, toluene, −10 °C (51%); (d) TBDMSCl, imid, DMF, 70 °C; (e) $NaBH_4$, $CeCl_3$, MeOH, 0 °C (78%); (f) *p*-$NO_2C_6H_4CO_2H$, DEAD, PPh_3, benzene, rt; (g) 10% HCl, MeOH, rt; (h) Dess−Martin periodinane, CH_2Cl_2, rt (80%); (i) K_2CO_3, MeOH, rt; (j) TBAF, THF, rt (82%).

temperature. Although substrate **36** for the inversion reaction was used as a mixture of two diastereoisomers, the isolated **36** and the inverted product **37** were both apparently a single stereoisomer, the stereochemistries of which were undetermined. This result obviously indicated that one of two diastereoisomers of **36** reacted readily with the Mitsunobu reagents to provide the desired **37**, while the other isomer was inactive toward those reagents. The chemical yield of **37** (45%) was not good enough; nevertheless, we took this compound forward to the final stage of the synthesis of **2**. Removal of the TBDMS group of **37** under acidic conditions gave the corresponding hydroxyl derivative, which was then oxidized with Dess−Martin periodinane to afford **38** in 80% yield. Finally successive treatment of **38** with potassium carbonate and TBAF produced (±)-8α-hydroxystreptazolone (**2**) in 82% yield. The synthetic racemic 8α-hydroxystreptazolone (**2**) was identical to the natural compound based on a comparison of their ^1H and ^{13}C NMR spectra.

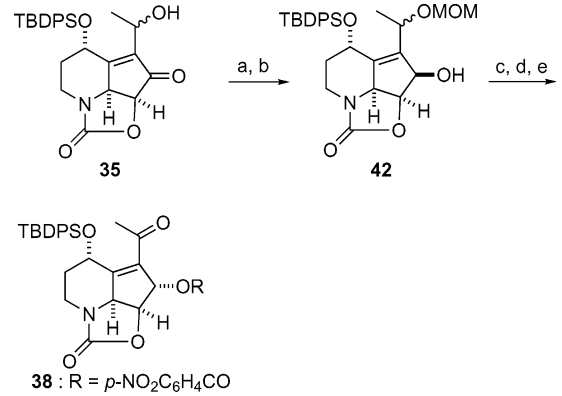
The first total synthesis of (±)-**2** from 2-oxazolone was thus accomplished. One-half of the synthetic intermediate **36**, however, could not be converted into**2**. This step might have made this total synthesis less efficient. Therefore, an alternative procedure was necessary to transform **36** into **37**. One of two diastereoisomers of **36** did not react with the Mitsunobu reagent which might indicate steric congestion by the bulky TBDMS group, although this was unclear. We envisioned constructing an essential acetyl functionality at the C_6-position prior to inverting the stereochemistry at the C_7-position. Thus, compound **36** was converted into the corresponding acetyl derivative **40** as shown in Scheme 7. Treatment of **40** with the Mitsunobu reagents under various conditions,

SCHEME 7[a]



[a] Reaction conditions: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C; 10% HCl, MeOH, rt; (c) Dess−Martin periodinane, CH_2Cl_2, rt (50%); (d) K_2CO_3, MeOH, rt (96%); (e) TBAF, THF, rt (83%).

SCHEME 8[a]



[a] Reaction conditions: (a) MOMCl, $^iPr_2NEt$, CH_2Cl_2, reflux; (b) $NaBH_4$, $CeCl_3$, MeOH, 0 °C (90%); (c) p-$NO_2C_6H_4CO_2H$, PPh_3, DEAD, benzene, 60 °C; (d) concd HCl, THF, 60 °C; (e) Dess-Martin periodinane, CH_2Cl_2, rt (65%).

however, led to the recovery of the starting material **40**.[23] The intramolecular hydrogen bonding between the C_6-acetyl carbonyl oxygen and the C_7-hydroxyl group presumably caused farily low reactivity toward the Mitsunobu reagents. It should be mentioned here that desilylation of **40** with TBAF afforded (±)-7-*epi*-8α-hydroxystreptazolone (**41**)[4] in 83% yield, although its isolation has not been reported.

On the basis of these results, we decided to change the protecting group on the secondary hydroxyl group of the tricyclic compound, such as **37** in Scheme 6, from the bulky TBDMS group to the less sterically hindered methoxymethyl (MOM) group (Scheme 8). Protection of the hydroxyl group of the tricyclic compound **35**, obtained from the Pauson−Khand reaction, with the MOM group was followed by stereoselective reduction to give **42** in 90% yield. The Mitsunobu reaction of **42**, which required 60 °C for completion of the reaction,[24] afforded the inverted products, which were subsequently exposed to concentrated HCl and Dess−Martin periodinane to produce **38** in 65% overall yield. Thus, the transformation of **36** into **37** was improved by changing the protecting group on the secondary hydroxyl moiety.

In summary, we have developed a novel and efficient procedure for constructing 7-hydroxy-6-substituted-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-ene-7,10-diones (e.g., **16**, **31**, and **35**) by the intramolecular Pauson-Khand reaction of the 2-oxazolone species with the required alkyne appendages. In addition, by taking advantage of this newly developed method, we have achieved the first total synthesis of (±)-8α-hydroxystreptazolone (**2**) in a highly stereoselective manner. Synthesis of (±)-7-*epi*-8α-hydroxystreptazolone (**41**)[4] was also achieved. Since the tricyclic compound **35** has the entire carbon framework and suitable functionalities for further elaborations, it should be a versatile intermediate for the synthesis of streptazolin and its related natural products. Studies on the conversion of **35** into other related natural products are now in progress.

Experimental Section

5-(*tert*-Butyldimethylsiloxy)-1-trimethylsilyl-1-pentyn-3-ol (11). To a solution of **10** (4.75 g, 25.0 mmol), DMSO (5.30 mL, 75.0 mmol), and Et_3N (10.4 mL, 75.0 mmol) in dry CH_2Cl_2 (100 mL) was added SO_3·pyridine (11.9 g, 75.0 mmol) at 0 °C. After being stirred for 1 h, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to afford the crude aldehyde. To a solution of trimethylsilylacetylene (5.30 mL, 37.5 mmol) in dry THF (100 mL) was added ^{n}BuLi in hexane (1.43 M, 21.0 mL, 29.7 mmol) at −78 °C. After being stirred for 1 h, a solution of the crude aldehyde in THF (20 mL) was added to the reaction mixture, which was then stirred for 3 h. The reaction mixture was quenched by addition of water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (15:1) to afford **11** (5.36 g, 75%) as a pale yellow oil: IR 3600, 3455, 2170 cm^{-1}; ^{1}H NMR δ 4.66−4.53 (m, 1H), 4.10−3.98 (m, 1H), 3.89−3.76 (m, 1H), 3.44−3.30 (m, 1H), 2.07−1.78 (m, 2H), 0.90 (s, 9H), 0.17 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR δ 106.2, 89.2, 62.2, 61.0, 38.4, 25.8, 18.13, −0.1, −5.6, −5.6; FABMS m/z 287 ($M^+ + 1$, 1.9); HRMS calcd for $C_{14}H_{30}O_2Si_2$ 286.1784, found 286.1778.

5-(*tert*-Butyldimethylsiloxy)-3-(*tert*-butyldiphenylsiloxy)-1-pentyne (13). To a solution of **11** (660 mg, 2.30 mmol) in MeOH (20 mL) was added K_2CO_3 (410 mg, 3.00 mmol) at room temperature. The reaction mixture was stirred for 2 h, and MeOH was evaporated off. The residue was diluted with water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (30:1) to afford the known **12**[14] (480 mg, 97%) as a colorless oil: IR 3467, 3307 cm^{-1}; ^{1}H NMR δ 4.68−4.55 (m, 1H), 4.12−4.00 (m, 1H), 3.89−3.78 (m, 1H), 3.50 (brs, 1H), 2.46 (d, 1H, J = 2.0 Hz), 2.08−1.80 (m, 2H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR δ 84.4, 72,8, 61.7, 61.0, 38.3, 25.8, 18.1, −5.6. To a solution of **12** (480 mg, 2.23 mmol) in dry DMF (0.8 mL) were added imidazole (297 mg, 4.36 mmol) and TBDPSCl (0.87 mL, 3.27 mmol) at room temperature. After being stirred for 5 h, the reaction mixture was quenched by addition of water and

(23) In some cases, a trace amount of the inverted compound could be detected.

(24) The reaction did not occur at room temperature.

extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (30:1) to afford **13** (1.00 g, 99%) as a colorless oil: IR 3307 cm^{-1}; ^1H NMR δ 7.78−7.64 (m, 4H), 7.47−7.30 (m, 6H), 4.54 (dt, 1H, J = 6.6, 2.0 Hz), 3.74 (t, 2H, J = 6.6 Hz), 2.28 (d, 1H, J = 2.0 Hz), 2.05−1.80 (m, 2H), 1.08 (s, 9H), 0.81 (s, 9H), −0.02 (s, 3H), −0.03 (s, 3H); ^{13}C NMR δ 136.0, 135.8, 133.5, 133.4, 129.7, 129.6, 127.6, 127.4, 84.7, 73.0, 61.1, 59.2, 41.4, 26.9, 25.9, 19.3, 18.2, −5.4, −5.4; MS m/z 452 (M^+, 0.1); FABHRMS calcd for $C_{27}H_{41}O_2Si_2$ 453.2645, found 453.2650. Anal. Calcd for $C_{27}H_{40}O_2Si_2$: C, 71.62; H, 8.90. Found: C, 71.47; H, 8.84.

5-(*tert*-Butyldiphenylsiloxy)-7-iodo-3-heptyne (14). To a solution of **13** (2.50 g, 5.53 mmol) in dry THF (50.0 mL) was added ^{n}BuLi (1.23 M hexane solution, 9.0 mL, 11.0 mmol) at −35 °C. After the mixture was stirred for 30 min, ethyl iodide (1.80 mL, 22.0 mmol) was added, and the mixture was gradually warmed to 45 °C. The reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. To a solution of the crude product in MeOH (50 mL) was added PPTS (138 mg, 0.55 mmol) at room temperature. After being stirred for 10 h, MeOH was evaporated off, and the residue was diluted with water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (10:1) to afford crude alcohol. To a solution of the crude alcohol in dry CH_2Cl_2 (50.0 mL) were added PPh_3 (1.47 g, 5.60 mmol) and imidazole (381 mg, 5.60 mmol) at room temperature. I_2 (1.42 g, 5.60 mmol) was then added to the reaction mixture, which was stirred for 3 h at room temperature. CH_2Cl_2 was evaporated off, and the residue was chromatographed with hexane−AcOEt (10:1) to afford **14** (1.80 g, 69%) as a colorless oil: ^1H NMR δ 7.79−7.66 (m, 4H), 7.48−7.32 (m, 6H), 4.42 (tt, 1H, J = 5.9, 2.0 Hz), 3.33−3.22 (m, 2H), 2.23−2.12 (m, 2H), 2.00 (qd, 2H, J = 7.6, 2.0 Hz), 1.07 (s, 9H), 0.94 (t, 3H, J = 7.6 Hz); ^{13}C NMR δ 136.0, 135.9, 133.8, 133.4, 129.7, 129.5, 127.6, 127.3, 87.9, 79.2, 64.3, 42.4, 26.9, 19.3, 13.4, 12.3, 1.0; FABMS m/z 477 (M^+ + 1, 0.75); FABHRMS calcd for $C_{23}H_{30}IOSi$ 477.1111, found 477.1103. Anal. Calcd for $C_{23}H_{29}IOSi$: C, 57.98; H, 6.13. Found: C, 58.26; H, 6.21.

3-[(3-*tert*-Butyldiphenylsiloxy)-4-heptynyl]-2-oxazolone (15). To a solution of 2-oxazolone[25] (20.4 mg, 0.24 mmol) in dry DMF (3.0 mL) was added NaH (14.0 mg, 0.35 mmol) at 0 °C. After being stirred for 30 min, a solution of **14** (76.0 mg, 0.16 mmol) in DMF (2.0 mL) was added to the reaction mixture, which was stirred at room temperature for 12 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (4:1) to afford **15** (59.4 mg, 86%) as a colorless oil: IR 1747 cm^{-1}; ^1H NMR δ 7.82−7.63 (m, 4H), 7.50−7.32 (m, 6H), 6.70 (d, 1H, J = 2.0 Hz), 6.36 (d, 1H, J = 2.0 Hz), 4.41 (tt, 1H, J = 5.6, 2.0 Hz), 3.74 (t, 2H, J = 7.3 Hz), 2.11−1.90 (m, 4H), 1.08 (s, 9H), 0.98 (t, 3H, J = 7.6 Hz); ^{13}C NMR δ 155.5, 136.0, 135.7, 133.5, 133.3, 129.9, 129.6, 127.7, 127.4, 127.2, 116.0, 88.2, 79.1, 61.5, 40.4, 37.0, 26.9, 19.2, 13.4, 12.3; MS m/z 433 (M^+, 0.36); FABHRMS calcd for $C_{26}H_{32}NO_3Si$ 434.2151, found 434.2146. Anal. Calcd for $C_{26}H_{31}NO_3Si$: C, 72.02; H, 7.21; N, 3.23. Found: C, 71.84; H, 7.26; N, 3.19.

(4*R,8*R**,11*R**)-4-(*tert*-Butyldiphenylsiloxy)-6-ethyl-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-ene-7,10-dione (16).** To a solution of **15** (40.7 mg, 0.94 × 10^{-1} mmol) in Et_2O (10 mL) was added $Co_2(CO)_8$ (48.1 mg, 0.14 mmol) at room temperature. After the mixture was stirred for 1 h, Et_2O was evaporated off, and the residue was passed through a short pad of silica gel with hexane−AcOEt (5:1) to afford the crude cobalt complex. To a solution of the crude cobalt complex in dry THF was added TMANO·$2H_2O$ (37.4 mg, 0.33 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was passed through a short pad of Celite and concentrated to dryness. The residual oil was chromatographed with hexane−AcOEt (5:1) to afford **16** (16.0 mg, 37%) as a colorless oil: IR 1759, 1726, 1652 cm^{-1}; ^1H NMR δ 7.69−7.31 (m, 10H), 4.98 (dd, 1H, J = 3.4, 2.0 Hz), 4.88 (d, 1H, J = 6.4 Hz), 4.54 (d, 1H, J = 6.4 Hz), 3.85−3.71 (m, 2H), 1.98−1.83 (m, 2H), 1.71−1.58 (m, 2H), 1.11 (s, 9H), 0.76 (t, 3H, J = 7.3 Hz); ^{13}C NMR δ 199.6, 165.9, 156.0, 137.9, 135.5, 132.4, 130.4, 128.1, 127.9, 71.4, 64.7, 55.2, 37.5, 36.7, 26.9, 19.3, 16.1, 12.3; MS m/z 461 (M^+, 2.7); HRMS calcd for $C_{27}H_{31}NO_4Si$ 461.2023, found 461.2021. Anal. Calcd for $C_{27}H_{31}NO_4Si$: C, 70.25; H, 6.77; N, 3.03. Found: C, 70.27; H, 7.12; N, 2.91.

Ring Closure of 15 with TMANO and 4 Å MS in Toluene (Table 2, Entry 7). To a solution of **15** (63.4 mg, 0.15 mmol) in Et_2O (10 mL) was added $Co_2(CO)_8$ (74.9 mg, 0.22 mmol) at room temperature. After being stirred for 1 h, Et_2O was evaporated off, and the residue was passed through a short pad of silica gel with hexane−AcOEt (5:1) to afford the crude cobalt complex. To a solution of the crude cobalt complex and 4 Å MS (507 mg) in dry toluene (2.0 mL) was added TMANO (50.0 mg, 0.67 mmol) at −10 °C. After being stirred at −10 °C for 12 h, the reaction mixture was passed through a short pad of Celite and concentrated to dryness. The residual oil was chromatographed with hexane−AcOEt (5:1) to afford **16** (40.2 mg, 60%).

(4*R,7*R**,8*R**,11*R**)-4-Acetoxy-6-ethyl-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-ene-7,10-dione (17).** To a solution of **16** (55.0 mg, 0.12 mmol) in dry THF (1.5 mL) was added TBAF (1.00 M solution in THF, 0.14 mL, 0.14 mmol) at room temperature. After being stirred for 30 min, THF was evaporated off, and the residue was passed through a short pad of silica gel with hexane−AcOEt (1:2) to afford the crude alcohol. To a solution of the crude alcohol and DMAP (1.00 mg, 0.08 × 10^{-1} mmol) in dry CH_2Cl_2 (1.5 mL) were added Et_3N (0.03 mmol, 0.21 mmol) and Ac_2O (0.02 mL, 0.21 mmol) at 0 °C. After being stirred for 2 h, CH_2Cl_2 was evaporated off, and the residue was chromatographed with hexane−AcOEt (2:1) to afford **17** (24.9 mg, 79%) as colorless needles: mp 133−134 °C (hexane−AcOEt); IR 1761, 1731, 1654 cm^{-1}; ^1H NMR δ 5.85 (t, 1H, J = 2.9 Hz), 4.65 (d, 1H, J = 6.4 Hz), 4.57 (d, 1H, J = 6.4 Hz), 3.85 (ddd, 1H, J = 14.2, 5.9, 1.0 Hz), 3.54 (ddd, 1H, J = 14.2, 12.7, 3.4 Hz), 2.34 (q, 2H, J = 7.3 Hz), 2.17−2.10 (m, 1H), 2.14 (s, 3H), 1.96−1.86 (m, 1H), 1.05 (t, 3H, J = 7.3 Hz); ^{13}C NMR δ 199.0, 169.7, 161.0, 155.8, 141.1, 71.4, 65.4, 55.1, 37.5, 33.0, 20.7, 16.4, 12.5. MS m/z 265 (M^+, 3.3); HRMS calcd for $C_{13}H_{15}NO_5$ 265.0951, found 265.0951. Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.72; H, 5.75; N, 5.11.

(4*R,7*S**,8*R**,11*R**)-4-(*tert*-Butyldiphenylsiloxy)-6-ethyl-7-hydroxy-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-en-10-one (21).** To a solution of **16** (4.6 mg, 0.01 mmol) in MeOH (0.50 mL) were added $CeCl_3$ (3.7 mg, 0.15 × 10^{-1} mmol) and $NaBH_4$ (1.0 mg, 0.26 × 10^{-1} mmol) at 0 °C. After being stirred for 30 min, MeOH was evaporated off, and the residue was chromatographed with hexane−AcOEt (3:1) to afford **21** (4.60 mg, 100%) as colorless oil: IR 3566, 1750 cm^{-1}; ^1H NMR δ 7.68−7.61 (m, 2H), 7.59−7.53 (m, 2H), 7.49−7.32 (m, 6H), 4.85−4.77 (m, 2H), 4.73 (t, 1H, J = 2.9 Hz), 4.69 (d, 1H, J = 5.9 Hz), 3.74−3.63 (m, 2H), 2.38−2.30 (m, 1H), 1.78 (q, 2H, J = 7.3 Hz), 1.74−1.68 (m, 1H), 1.62−1.54 (m, 1H), 1.07 (s, 9H), 0.80 (t, 3H, J = 7.3 Hz); ^{13}C NMR δ 157.8, 138.7, 135.6, 133.3, 133.2, 130.0, 129.9, 127.8, 127.6, 78.4, 74.1, 64.1, 61.2, 38.4, 35.3, 26.9, 19.3, 17.9, 12.0; MS m/z 463 (M^+, 0.88); HRMS calcd for $C_{27}H_{33}NO_4Si$ 463.2179, found 463.2174.

(4*R,7*S**,8*R**,11*R**)-7-Acetoxy-4-(*tert*-butyldiphenylsiloxy)-6-ethyl-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-en-10-one (22).** Compound **16** (18.7 mg, 0.04 mmol) was first

(25) (a) Scholz, K. H.; Heine, H. G.; Hartmann, W. *Justus Liebigs Ann. Chem.* **1976**, 1319. (b) Kunieda, T.; Abe, Y.; Iitaka, Y.; Hirobe, M. *J. Org. Chem.* **1982**, *47*, 4291. (c) Ho, G.-J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271.

converted into **21**. To a solution of crude **21** and DMAP (1.00 mg, 0.08 × 10^{-1} mmol) in dry CH_2Cl_2 were added Ac_2O (0.02 mL, 0.21 mmol) and Et_3N (0.03 mL, 0.21 mmol) at room temperature. After being stirred for 2 h, CH_2Cl_2 was evaporated off, and the residue was chromatographed with hexane−AcOEt (4:1) to afford **22** (20.0 mg, 99%) as colorless needles: mp 135−136 °C (hexane−AcOEt); IR 1744 cm^{-1}; ^1H NMR δ 7.68−7.62 (m, 2H), 7.59−7.54 (m, 2H), 7.49−7.33 (m, 6H), 5.59 (d, 1H, J = 4.9 Hz), 5.04 (dd, 1H, J = 6.4, 4.9 Hz), 4.76 (t, 1H, J = 2.9 Hz), 4.72 (d, 1H, J = 6.4 Hz), 3.77−3.63 (m, 2H), 2.11 (s, 3H), 1.79−1.68 (m, 3H), 1.64−1.54 (m, 1H), 1.08 (s, 9H), 0.72 (t, 3H, J = 7.3 Hz); ^{13}C NMR δ 170.6, 157.9, 136.1, 135.6, 134.3, 133.2, 130.1, 130.0, 127.9, 127.7, 79.6, 72.6, 64.0, 61.4, 38.2, 35.3, 26.9, 20.5, 19.3, 18.0, 12.0; FABMS m/z 506 (M^+ + 1, 2.0); HRMS calcd for $C_{29}H_{35}NO_5Si$ 505.2284, found 505.2278. Anal. Calcd for $C_{29}H_{35}NO_5Si$: C, 68.88; H, 6.98; N, 2.77. Found: C, 68.90; H, 7.18; N, 2.77.

(4*R,7*S**,8*R**,11*R**)-4-(*tert*-Butyldiphenylsiloxy)-6-ethyl-7-(*p*-nitrobenzoyloxy)-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-en-10-one (23).** Compound **16** (14.4 mg, 0.03 mmol) was first converted into **21**. To a solution of crude **21** and DMAP (1.00 mg, 0.008 mmol) in dry CH_2Cl_2 were added *p*-nitrobenzoyl chloride (8.40 mg, 0.45 × 10^{-1} mmol) and Et_3N (0.03 mL, 0.2 1 mmol). After being stirred for 3 h, CH_2Cl_2 was evaporated off, and the residue was chromatographed with hexane−AcOEt (4:1) to afford **23** (18.2 mg, 96%) as pale yellow needles: mp 136−137 °C (hexane−AcOEt); IR 1751, 1732 cm^{-1}; ^1H NMR δ 8.30−8.24 (m, 2H), 8.22−8.17 (m, 2H), 7.70−7.64 (m, 2H), 7.62−7.57 (m, 2H), 7.51−7.35 (m, 6H), 5.89 (d, 1H, J = 4.9 Hz), 5.17 (dd, 1H, J = 6.4, 4.9 Hz), 4.82 (t, 1H, J = 2.9 Hz), 4.81 (d, 1H, J = 6.4 Hz), 3.80−3.66 (m, 2H), 1.88−1.74 (m, 3H), 1.70−1.61 (m, 1H), 1.10 (s, 9H), 0.78 (t, 3H, J = 7.3 Hz); ^{13}C NMR δ 164.3, 157.7, 150.7, 137.1, 135.6, 134.7, 133.6, 133.1, 133.0, 131.0, 130.2, 130.1, 127.9, 127.7, 123.6, 80.9, 72.5, 64.0, 61.5, 38.2, 35.3, 26.9, 19.3, 18.2, 12.2; MS m/z 612 (M^+, 0.7); HRMS calcd for $C_{34}H_{36}N_2O_7Si$ 612.2292, found 612.2285. Anal. Calcd for $C_{34}H_{36}N_2O_7Si$: C, 66.65; H, 5.92; N, 4.57. Found: C, 66.66; H, 6.15; N, 4.52.

(4*R,7*R**,8*R**,11*R**)-4-(*tert*-Butyldiphenylsiloxy)-6-ethyl-7-(*p*-nitrobenzoyloxy)-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-en-10-one (24).** Compound **16** (23.0 mg, 0.05 mmol) was first converted into **21**. To a solution of crude **21** in dry benzene (0.04 mL) were added PPh_3 (39.0 mg, 0.15 mmol) and *p*-nitrobenzoic acid (25.0 mg, 0.15 mmol) at room temperature. DEAD (23.0 μL, 0.15 mmol) was added to the reaction mixture, which was then stirred for 4 h at room temperature. Benzene was evaporated off, and the residue was chromatographed with hexane−AcOEt (4:1) to afford **24** (29.0 mg, 94%) as colorless needles: mp 151.5−152.5 °C (hexane−AcOEt); IR 1751 cm^{-1}; ^1H NMR δ 8.40−8.31 (m, 2H), 8.23−8.14 (m, 2H), 7.75−7.58 (m, 4H), 7.52−7.27 (m, 6H), 5.80 (s, 1H), 5.03 (d, 1H, J = 6.3 Hz), 4.85−4.75 (m, 1H), 4.80 (d, 1H, J = 6.3 Hz), 3.88−3.60 (m, 2H), 1.96−1.80 (m, 1H), 1.77−1.40 (m, 3H), 1.11 (s, 9H), 0.80 (t, 3H, J = 7.6 Hz); ^{13}C NMR δ 163.7, 156.8, 150.8, 141.1, 135.6, 135.6, 134.8, 133.1, 133.0, 130.8, 130.1, 129.9, 127.9, 127.7, 123.7, 84.1, 77.3, 64.3, 61.7, 37.9, 35.3, 26.9, 19.3, 18.5, 12.2; FABMS m/z 613 (M^+ + 1, 19); FABHRMS calcd for $C_{34}H_{36}N_2O_7Si$ 613.2370, found 613.2365. Anal. Calcd for $C_{34}H_{36}N_2O_7Si$: C, 66.65; H, 5.92; N, 4.57. Found: C, 66.68; H, 6.13; N, 4.48.

3-[3-(*tert*-Butyldiphenylsiloxy)-6-hydroxy-4-heptynyl]-2-oxazolone (34). To a solution of **28** (175 mg, 0.43 mmol) in dry THF (5.0 mL) was added NaHMDS (1.00 M solution in THF, 0.86 mL, 0.86 mmol) at −78 °C. After the mixture was stirred for 30 min, acetaldehyde (0.20 mL, 3.60 mmol) was added, and the mixture was then warmed to room temperature over a period of 2 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (2:1) to afford **34** (165 mg, 86%) as a colorless oil: IR 3595, 3447, 1747 cm^{-1}; ^1H NMR δ 7.78−7.62 (m, 4H), 7.49−7.33 (m, 6H), 6.72 (d, 1H, J = 2.0 Hz), 6.38 (d, 1H × 50/100, J = 2.0 Hz), 6.37 (d, 1H × 50/100, J = 2.0 Hz), 4.50−4.39 (m, 1H), 4.37−4.21 (m, 1H), 3.89−3.65 (m, 2H), 2.09−1.93 (m, 3H), 1.23 (d, 3H, J = 6.6 Hz), 1.07 (s, 9H); ^{13}C NMR δ 155.5, 135.9, 135.7, 133.3, 133.2, 132.9, 132.8, 129.9, 129.7, 127.7, 127.4, 127.4, 115.8, 88.4, 83.0, 82.9, 61.1, 57.7, 40.2, 36.5, 26.8, 23.7, 23.6, 19.1; FABMS m/z 450 (M^+ + 1, 2.2); FABHRMS calcd for $C_{26}H_{32}NO_4Si$ 450.2101, found 450.2100. Anal. Calcd for $C_{26}H_{31}NO_4Si$: C, 69.45; H, 6.95; N, 3.12. Found: C, 69.07; H, 7.11; N, 3.06.

(4*R,8*R**,11*R**,1′*R**)- and (4*R**,8*R**,11*R**,1′*S**)-4-(*tert*-Butyldiphenylsiloxy)-6-(1′-hydroxyethyl)-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-ene-7,10-dione (35).** According to the Pauson−Khand conditions with TMANO and 4 Å MS in toluene (Table 2, entry 7), **34** (65.0 mg, 0.14 mmol) was converted into **35** (34.9 mg, 51%) as colorless needles: mp 172.5−173.5 °C (hexane−AcOEt); IR 3564, 3447, 1759, 1720, 1649 cm^{-1}; ^1H NMR δ 7.74−7.32 (m, 10H), 5.48 (dd, 1H × 40/100, J = 3.6, 1.7 Hz), 5.30 (dd, 1H × 60/100, J = 3.6, 1.7 Hz), 4.95 (d, 1H, J = 6.3 Hz), 4.56 (d, 1H, J = 6.3 Hz), 4.33−4.18 (m, 1H), 3.88−3.67 (m, 2H), 2.05−1.63 (m, 2H), 1.14−1.06 (m, 3H), 1.12 (s, 9H); ^{13}C NMR δ 199.5, 199.0, 167.3, 167.0, 155.8, 138.3, 138.0, 135.6, 132.9, 132.5, 132.3, 130.4, 130.4, 128.0, 127.9, 127.8, 71.4, 64.6, 63.4, 63.2, 55.1, 55.0, 37.2, 36.7, 36.3, 26.9, 26.7, 22.3, 21.8, 19.3; FABMS m/z 478 (M^+ + 1, 19). FABHRMS calcd for $C_{27}H_{32}NO_5Si$ 478.2050, found 478.2087. Anal. Calcd for $C_{27}H_{31}NO_5Si$: C, 67.90; H, 6.54; N, 2.93. Found: C, 67.62; H, 6.63; N, 2.85.

(4*R,7*S**,8*R**,11*R**,1′*R**)- and (4*R**,7*S**,8*R**,11*R**,1′*S**)-6-[1′-(*tert*-Butyldimethylsiloxy)ethyl]-4-(*tert*-butyldiphenylsiloxy)-7-hydroxy-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-en-10-one (36).** To a solution of **35** (23.0 mg, 0.48 × 10^{-1} mmol) in dry DMF (0.02 mL) were added TBDMSCl (24.0 mg, 0.16 mmol) and imidazole (11 mg, 0.16 mmol). The reaction mixture was stirred at 70 °C for 1 h, quenched by addition of water, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. To a solution of the crude product in MeOH (2.0 mL) were added $NaBH_4$ (2.20 mg, 0.58 × 10^{-1} mmol) and $CeCl_3$ (16.0 mg, 0.64 × 10^{-1} mmol) at 0 °C. The reaction mixture was stirred for 30 min, and MeOH was evaporated off. The reaction mixture was quenched by addition of water, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (3:1) to afford **36** (22.0 mg, 78%) as a colorless oil: IR 3560, 3487, 1751 cm^{-1}; ^1H NMR δ 7.70−7.30 (m, 10H), 5.36 (t, 1H × 50/100, J = 2.6 Hz), 5.05 (dd, 1H × 50/100, J = 7.3, 4.6 Hz), 4.88−4.74 (m, 4H × 50/100), 4.67 (t, 1H × 50/100, J = 2.6 Hz), 4.62 (d, 1H × 50/100, J = 6.3 Hz), 4.48 (q, 1H × 50/100, J = 6.6 Hz), 4.07 (q, 1H × 50/100, J = 6.3 Hz), 3.82−3.58 (m, 2H), 3.47 (d, 1H × 50/100, J = 7.3 Hz), 2.51 (m, 1H × 50/100), 1.81−1.64 (m, 2H), 1.10−1.03 (m, 3H × 50/100), 1.08 (s, 9H × 50/100), 1.06 (s, 9H × 50/100), 1.01 (d, 3H × 50/100, J = 6.3 Hz), 0.76 (s, 9H × 50/100), 0.69 (s, 9H × 50/100), −0.10 (s, 3H × 50/100), −0.11 (s, 3H × 50/100), −0.15 (s, 3H × 50/100), −0.18 (s, 3H × 50/100); ^{13}C NMR δ 158.4, 157.7, 140.0, 136.3, 135.7, 135.6, 135.6, 134.3, 134.2, 133.4, 133.1, 133.0, 130.2, 130.1, 130.0, 129.8, 127.9, 127.8, 127.8, 127.6, 78.3, 75.0, 73.8, 65.7, 64.4, 64.1, 63.8, 61.2, 61.0, 38.2, 38.1, 35.0, 34.9, 27.0, 26.9, 25.7, 25.6, 23.3, 21.1, 19.4, 19.2, 17.9, 17.6, −4.7, −5.0, −5.1; FABMS m/z 594 (M^+ + 1, 18); FABHRMS calcd for $C_{33}H_{48}NO_5Si_2$ 594.3071, found 594.3046. Anal. Calcd for $C_{33}H_{47}NO_5Si_2$: C, 66.74; H, 7.98; N, 2.36. Found: C, 66.36; H, 8.09; N, 2.35.

(4*R,7*R**,8*R**,11*R**)-6-[1′-(*tert*-Butyldimethylsiloxy)-ethyl]-4-(*tert*-butyldiphenylsiloxy)-7-(*p*-nitrobenzoyloxy)-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-en-10-one (37).** To a solution of **36** (20.5 mg, 0.04 mmol) in dry benzene (0.08 mL) were added PPh_3 (27.2 mg, 0.10 mmol) and *p*-$NO_2C_6H_4CO_2H$ (17.4 mg, 0.10 mmol) at room temperature. DEAD (0.02 mL, 0.13 mmol) was then added to the reaction mixture, which was stirred at 70 °C for 2 h. The reaction mixture was directly

chromatographed with hexane−AcOEt (5:1) to afford **37** (11.6 mg, 45%) and recovered starting material **36** (10.2 mg, 50%) as a single isomer: Compound **37** was colorless needles:, mp 104−105 °C (hexane−AcOEt); IR 1755, 1734 cm^{-1}; ^1H NMR δ 8.36−8.30 (m, 2H), 8.21−8.15 (m, 2H), 7.71−7.62 (m, 4H), 7.49−7.32 (m, 6H), 5.91 (s, 1H), 5.20 (dd, 1H, J = 3.4, 2.0 Hz), 5.13 (d, 1H, J = 5.9 Hz), 4.75 (d, 1H, J = 5.9 Hz), 4.34 (q, 1H, J = 6.4 Hz), 3.83−3.62 (m, 2H), 1.79−1.72 (m, 1H), 1.60−1.50 (m, 1H), 1.13 (s, 9H), 0.94 (d, 3H, J = 6.4 Hz), 0.63 (s, 9H), −0.13 (s, 3H), −0.23 (s, 3H); ^{13}C NMR δ 163.4, 156.8, 150.8, 142.7, 135.7, 135.6, 135.0, 134.9, 133.2, 133.0, 130.9, 130.2, 130.0, 127.9, 127.7, 123.6, 84.1, 77.3, 65.7, 64.6, 62.3, 37.9, 34.9, 27.0, 25.5, 24.7, 19.5, 17.7, −4.8, −5.2; FABMS m/z 743 (M^+ + 1, 1.8); FABHRMS calcd for $C_{40}H_{51}N_2O_8Si_2$ 743.7184, found 743.7196. Anal. Calcd for $C_{40}H_{50}N_2O_8Si_2$: C, 64.66; H, 6.78; N, 3.77. Found: C, 64.75; H, 6.96; N, 3.68; Recovered starting material **36** was a colorless oil: IR 3483, 1751 cm^{-1}; ^1H NMR δ 7.67−7.34 (m, 10H), 5.05 (dd, 1H, J = 7.3, 4.4 Hz), 4.79 (dd, 1H, J = 6.4, 4.4 Hz), 4.68 (t, 1H, J = 2.5 Hz), 4.62 (d, 1H, J = 6.4 Hz), 4.08 (q, 1H, J = 6.4 Hz), 3.74 (ddd, 1H, J = 13.7, 5.4, 1.5 Hz), 3.65 (td, 1H, J = 13.7, 2.9 Hz), 3.44 (d, 1H, J = 7.3 Hz), 1.79−1.63 (m, 2H), 1.07 (s, 9H), 1.04 (d, 3H, J = 6.4 Hz), 0.77 (s, 9H), −0.11 (s, 3H), −0.17 (s, 3H); ^{13}C NMR δ 158.4, 136.3, 135.6, 134.2, 133.1, 133.0, 130.2, 130.1, 127.9, 127.8, 78.3, 75.0, 64.1, 63.8, 61.0, 38.1, 34.9, 26.9, 25.6, 21.1, 19.3, 17.6, −4.7, −5.1; FABMS m/z 594 (M^+ + 1, 9.0); FABHRMS calcd for $C_{33}H_{48}NO_5Si_2$ 594.3071, found 594.3079. Anal. Calcd for $C_{33}H_{47}NO_5Si_2$: C, 66.74; H, 7.98; N, 2.36. Found: C, 66.40; H, 8.11; N, 2.35.

(4*R,7*R**,8*R**,11*R**)-6-Acetyl-4-(*tert*-butyldiphenylsiloxy)-7-(*p*-nitrobenzoyloxy)-9-oxa-1-azatricyclo-[6.2.1.0^{5,11}]undec-5-en-10-one (38).** To a solution of **37** (16.8 mg, 0.23 × 10^{-1} mmol) in MeOH (2.0 mL) was added 10% HCl (0.04 mL) at room temperature. After the mixture was stirred for 24 h, MeOH was evaporated off, and the residue was passed through a short pad of Na_2SO_4. To a solution of the crude alcohol in dry CH_2Cl_2 (2.0 mL) was added Dess−Martin periodinane (19.2 mg, 0.45 × 10^{-1} mmol) at room temperature. After being stirred for 5 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was washed with aqueous $Na_2S_2O_3$ and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane-AcOEt (4:1) to afford **38** (11.3 mg, 80%) as colorless needles: mp 161−162 °C (hexane−AcOEt); IR 1761, 1734, 1693 cm^{-1}; ^1H NMR δ 8.35 (d, 2H, J = 8.3 Hz), 8.16 (d, 2H, J = 8.3 Hz), 7.68−7.60 (m, 4H), 7.50−7.28 (m, 6H), 6.05 (s, 1H), 5.62−5.56 (m, 1H), 5.24 (d, 1H, J = 6.4 Hz), 4.82 (d, 1H, J = 6.4 Hz), 3.88−3.65 (m, 2H), 2.02−1.94 (m, 1H), 1.91 (s, 3H), 1.76−1.64 (m, 1H), 1.14 (s, 9H); ^{13}C NMR δ 194.8, 163.4, 156.8, 156.2, 151.0, 135.7, 135.6, 134.3, 132.9, 132.6, 130.9, 130.3, 130.1, 127.9, 127.7, 123.8, 83.0, 76.7, 64.8, 62.5, 37.6, 35.9, 29.8, 26.9, 19.4; FABMS m/z 627 (M^+ + 1, 0.4); FABHRMS calcd for $C_{34}H_{35}N_2O_8Si$ 627.2163, found 627.2162.

(±)-8α-Hydroxystreptazolone (2). To a solution of **38** (3.5 mg, 0.56 × 10^{-2} mmol) in MeOH (1.5 mL) was added K_2CO_3 (1.00 mg, 0.72 × 10^{-2} mmol) at room temperature. After being stirred for 15 min, MeOH was evaporated off, and the residue was passed through a short pad of silica gel with hexane−AcOEt (2:1) to afford the crude alcohol. To a solution of the crude alcohol in dry THF (1.5 mL) was added TBAF (1.0 M THF solution, 0.02 mL, 0.02 mmol) at room temperature. After the mixture was stirred for 15 min, THF was evaporated off, and the residue was chromatographed with AcOEt to afford the title compound (1.10 mg, 82%) as a colorless oil: IR 3593, 3391, 1753, 1688 cm^{-1}; ^1H NMR δ 5.38 (t, 1H, J = 3.3 Hz), 5.07−4.98 (m, 2H), 4.70 (d, 1H, J = 6.3 Hz), 3.77−3.46 (m, 2H), 2.41 (s, 3H), 2.02−1.89 (m, 1H), 1.83−1.67 (m, 1H); ^1H NMR (CD_3OD) δ 5.41 (dd, 1H, J = 3.3, 2.6 Hz), 5.06 (dd, 1H, J = 6.3, 0.7 Hz), 4.94 (d, 1H, J = 0.7 Hz), 4.65 (d, 1H, J = 6.3 Hz), 3.69−3.45 (m, 2H), 2.39 (s, 3H), 1.97−1.84 (m, 1H), 1.73−1.54 (m, 1H); ^{13}C NMR δ 198.5, 156.8, 153.2, 133.6, 81.2, 79.3, 63.0, 61.6, 37.3, 34.2, 30.2; ^{13}C NMR (CD_3OD) δ 199.7, 159.1, 154.0, 134.8, 81.7, 81.6, 63.5, 63.1, 38.3, 35.7, 30.2; MS m/z 239 (M^+, 6.3); HRMS calcd for $C_{11}H_{13}NO_5$ 239.0794, found 239.0796.

(4*R,7*S**,8*R**,11*R**)-7-Acetoxy-6-acetyl-4-(*tert*-butyldiphenylsiloxy)-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-en-10-one (39).** To a solution of **36** (45.0 mg, 0.76 × 10^{-1} mmol) in dry CH_2Cl_2 (2.0 mL) were added DMAP (1.00 mg, 0.08 × 10^{-1} mmol) and Et_3N (0.03 mL, 0.21 mmol) at 0 °C. Ac_2O (0.02 mL, 0.21 mmol) was then added to the reaction mixture. After being stirred for 2 h, the reaction mixture was quenched by addition of water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (4:1) to afford the crude acetate. To a solution of the crude acetate in MeOH (2.0 mL) was added 10% HCl (0.06 mL) at room temperature. The reaction mixture was stirred for 12 h at room temperature, and MeOH was evaporated off. The residue was passed through a short pad of silica gel with hexane−AcOEt (2:1) to afford crude alcohol. To a solution of the crude alcohol in dry CH_2Cl_2 (2.0 mL) was added Dess−Martin periodinane (32.0 mg, 0.76 × 10^{-1} mmol) at room temperature. After being stirred for 24 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was washed with aqueous $Na_2S_2O_3$, water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (3:1) to afford **39** (20.0 mg, 50%) as a colorless oil: IR 1751, 1693, 1647 cm^{-1}; ^1H NMR δ 7.62−7.28 (m, 10H), 5.65 (d, 1H, J = 5.0 Hz), 5.51−5.43 (m, 1H), 5.06 (dd, 1H, J = 6.6, 5.0 Hz), 4.83 (d, 1H, J = 6.6 Hz), 3.86−3.63 (m, 2H), 2.09 (s, 3H), 2.06−1.74 (m, 2H), 1.84 (s, 3H), 1.07 (s, 9H); ^{13}C NMR δ 195.2, 170.2, 157.1, 151.4, 135.5, 135.5, 133.2, 132.4, 130.2, 129.5, 127.9, 127.8, 78.8, 71.9, 63.9, 61.5, 37.8, 36.0 29.3, 27.0, 20.4, 19.3; FABMS m/z 520 (M^+ + 1, 8.1);. FABHRMS calcd for $C_{29}H_{34}NO_6Si$ 520.2156, found 520.2136.

(4*R,7*S**,8*R**,11*R**)-6-Acetyl-4-(*tert*-butyldiphenylsiloxy)-7-hydroxy-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-en-10-one (40).** To a solution of **39** (1.70 mg, 0.03 × 10^{-1} mmol) in MeOH (1.0 mL) was added K_2CO_3 (0.5 mg, 0.03 × 10^{-1} mmol) at room temperature. After the mixture was stirred for 30 min, MeOH was evaporated off, and the residue was chromatographed with hexane−AcOEt (2:1) to afford **40** (1.50 mg, 96%) as a colorless oil: IR 3564, 1757 1690 cm^{-1}; ^1H NMR δ 7.60−7.29 (m, 10H), 5.40 (dd, 1H, J = 4.0, 2.0 Hz), 4.93 (dd, 1H, J = 11.2, 4.6 Hz), 4.87−4.77 (m, 2H), 3.80−3.64 (m, 2H), 2.59 (d, 1H, J = 11.2 Hz), 2.01 (s, 3H), 1.96−1.75 (m, 2H), 1.07 (s, 9H); ^{13}C NMR δ 197.4, 157.1, 148.2, 135.5, 134.0, 133.3, 132.5, 130.1, 130.1, 127.9, 127.7, 77.6, 73.6, 63.8, 61.2, 38.2, 36.1, 29.6, 27.0, 19.3; MS m/z 477 (M^+, 0.7); HRMS calcd for $C_{27}H_{31}NO_5$-Si 477.1971, found 477.1973.

(4*R,7*S**,8*R**,11*R**)-6-Acetyl-4,7-dihydroxy-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-en-10-one (41).** To a solution of **40** (60.0 mg, 0.13 mmol) in dry THF (5.0 mL) was added TBAF (1.0 M solution in THF, 0.15 mL, 0.15 mmol) at room temperature. After being stirred for 3 h, THF was evaporated off, and the residue was chromatographed with AcOEt−MeOH (20:1) to afford the title compound **41** (25.0 mg, 83%) as colorless needles: mp 166−167 °C (hexane−AcOEt); IR 3599, 3560, 3389, 1757, 1692 cm^{-1}; ^1H NMR δ 5.41 (brs, 1H), 5.28 (dd, 1H, J = 11.2, 5.0 Hz), 4.96 (dd, 1H, J = 6.6, 5.0 Hz), 4.83 (d, 1H, J = 6.6 Hz), 3.84−3.48 (m, 2H), 2.77 (d, 1H, J = 11.2 Hz), 2.41 (s, 3H), 2.02−1.80 (m, 2H), 1.90 (brs, 1H); ^1H NMR-(Acetone-d_6) δ 5.36 (dd, 1H, J = 10.6, 5.0 Hz), 5.26 (dd, 1H, J = 5.9, 3.0 Hz), 4.90 (dd, 1H, J = 6.3, 5.0 Hz), 4.80 (d, 1H, J = 6.3 Hz), 4.55 (d, 1H, J = 10.6 Hz), 4.43 (d, 1H, J = 3.0 Hz), 3.59−3.44 (m, 2H), 2.32 (s, 3H), 1.92−1.60 (m 2H); ^{13}C NMR(CD_3OD) δ 200.2, 160.2, 149.7, 136.4, 78.7, 76.7, 62.6, 62.5, 38.7, 35.9, 29.8; FABMS m/z 240 (M^+ + 1, 25); FABHRMS calcd for $C_{11}H_{14}NO_5$ 240.0872, found 240.0875.

(4*R,7*S**,8*R**,11*R**,1′*R**)- and (4*R**,7*S**,8*R**,11*R**,1′*S**)-4-(*tert*-Butyldiphenylsiloxy)-7-hydroxy-6-[1′-(methoxymethoxy)ethyl]-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-en-10-one (42).** To a solution of **35** (34.9 mg, 0.73 × 10^{-1} mmol) in dry CH_2Cl_2 (2.0 mL) were added MOMCl (0.02 mL, 0.26 mmol) and $^{i}Pr_2NEt$ (0.04 mL, 0.24 mmol) at room temperature. The reaction mixture was refluxed for 8 h, and CH_2Cl_2 was evaporated off. The residue was passed through a short pad of silica gel with hexane−AcOEt (2:1) to afford the crude MOM ether derivatives. To a solution of the crude products and $CeCl_3$ (23.4 mg, 0.095 mmol) in MeOH (2.0 mL) was added $NaBH_4$ (3.00 mg, 0.08 mmol) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C, and MeOH was evaporated off. The residue was diluted with water and extracted with AcOEt. The extract was washed with water, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (2:1) to afford **42** (34.4 mg, 90%) as colorless needles: mp 147−148 °C (hexane−AcOEt); IR 3564, 3479, 1751 cm^{-1}; ^1H NMR δ 7.69−7.52 (m, 4H), 7.50−7.32 (m, 6H), 5.15 (dd, 1H × 50/100, J = 3.4, 2.0 Hz), 4.97 (d, 1H × 50/100, J = 4.9 Hz), 4.90−4.75 (m, 5H × 50/100), 4.67 (d, 1H × 50/100, J = 6.3 Hz), 4.41 (d, 1H × 50/100, J = 6.8 Hz), 4.37 (d, 1H × 50/100, J = 6.8 Hz), 4.25−4.33 (m, 3H × 50/100), 3.92 (q, 1H × 50/100, J = 6.3 Hz), 3.77−3.62 (m, 2H), 3.17 (s, 3H × 50/100), 3.15 (s, 3H × 50/100), 1.82−1.54 (m, 2H), 1.11 (d, 3H × 50/100, J = 6.3 Hz), 1.08 (s, 9H × 50/100), 1.07 (s, 9H × 50/100), 1.04 (d, 3H × 50/100, J = 6.8 Hz); ^{13}C NMR δ 158.1, 157.8, 138.1, 137.9, 135.7, 135.6, 135.6, 135.5, 135.1, 134.6, 133.2, 133.1, 133.0, 130.1, 130.0, 129.9, 127.9, 127.8, 127.7, 127.6, 95.0, 94.2, 78.4, 78.1, 74.7, 74.0, 69.7, 67.1, 64.2, 63.8, 61.1, 60.9, 55.4, 55.1, 38.2, 38.1, 35.3, 35.0, 26.9, 26.9, 20.3, 19.3, 19.3, 18.1; FABMS m/z 524 (M^+ + 1, 3.0); FABHRMS calcd for $C_{29}H_{38}NO_6Si$ 524.2468, found 524.2450. Anal. Calcd for $C_{29}H_{37}NO_6Si$: C, 66.51; H, 7.12; N, 2.67. Found: C, 66.40; H, 7.08; N, 2.61.

Compound 38 from 42. To a solution of **42** (34.1 mg, 0.65 × 10^{-1} mmol) in dry benzene (0.03 mL) were added PPh_3 (51.2 mg, 0.20 mmol) and *p*-nitrobenzoic acid (32.7 mg, 0.20 mmol) at room temperature. DEAD (0.04 mL, 0.26 mmol) was then added to the reaction mixture, which was heated at 70 °C for 3 h. The reaction mixture was passed through a short pad of silica gel with hexane−AcOEt (4:1) to afford the crude *p*-nitrobenzoate. To a solution of the crude *p*-nitrobenzoate in dry THF (1.5 mL) was added concentrated HCl solution (0.40 mL) at room temperature. After being stirred for 3 h at 60 °C, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. To a solution of the crude alcohol in dry CH_2Cl_2 (1.5 mL) was added Dess−Martin periodinane (138 mg, 0.33 mmol) at room temperature. After being stirred for 12 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was washed with aqueous $Na_2S_2O_3$, water, and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (5:1) to afford **38** (26.3 mg, 65%).

Acknowledgment. We thank Drs. Y.-Q. Tang, D. Wunderlich, I. Sattler, and S. Grabley of the Hans-Knöll Institute of Natural Products Research, Germany, for generously providing ^1H and ^{13}C NMR spectra of the natural 8α-hydroxystreptazolone.

Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **2**, **11**, **21**, **25a**,**b**, **26a**, **32**, **34**, **38**, **39**, **40**, and **41**; preparation and characterization data for compounds **25a**−**d**, **26a**−**d**, **27**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0356816