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Total Synthesis of (±)-8α-Hydroxystreptazolone

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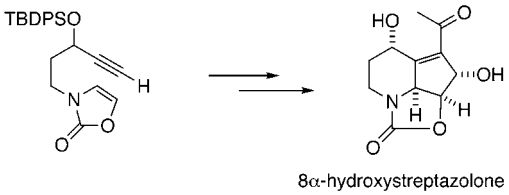
ABSTRACT



The intramolecular Pauson–Khand reaction of 2-oxazolone derivatives with a suitable pentynyl appendage exclusively gave the corresponding 4-hydroxy-6-substituted-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-en-7,10-diones. Based on 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.

Streptazolin (**1**) was first isolated from cultures 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] Its unique structural features as well as its promising biological activity profile have thus far led to four total syntheses.[3−6] The total synthesis of **1** was first reported by Kozikowski and Park[3] in a racemic form. Overman and Flann[4] completed an enantioselective synthesis of **1** starting from L-tartrate. Kibayashi and co-workers[5] also reported an enantioselective synthesis of **1** starting from L-tartrate by taking advantage of a palladium-mediated ring-closure reaction. In addition, the chiral auxiliary-mediated asymmetric synthesis of **1** was recently published by Comins and Huang.[6]

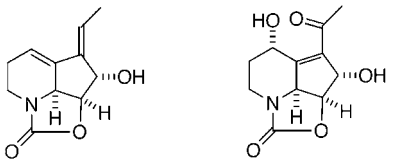


Figure 1.

Tang et al.[7] very recently reported the isolation of a streptazolin-dimer and three new streptazolin analogues, including 8α-hydroxystreptazolone (**2**)[8] together with streptazolin (**1**) and related known compounds[9] as secondary metabolites from *Streptomyces* sp. and *viridochromogenes* via chemical screening. As part of our program directed

(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) (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.

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

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

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

(7) Tang, Y.-Q.; Wunderlich, D.; Sattler, I.; Grabley, S.; Feng, X.-Z.; Thiericke, R. Abstract of Division of Organic Chemistry, Presented at the 223rd National Meeting of the American Chemical Society, Orlando, FL, April, 2002; p 341.

(8) Tang et al. called compound **2** 8α-hydroxystreptazolone.[7] 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.

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

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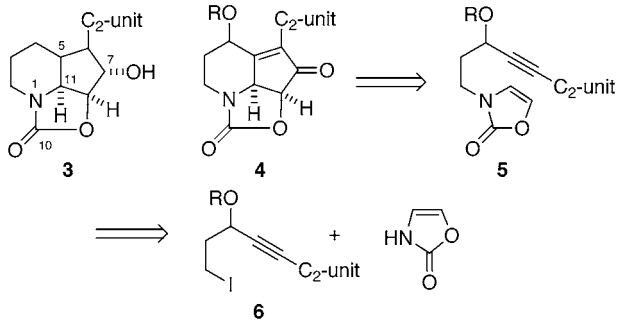
toward the development of stereoselective Pauson−Khand reactions[10] and their application to the total synthesis of natural products,[11] we have given considerable attention to the total synthesis of streptazolin and its related natural products via the Pauson−Khand reaction. A general retrosynthetic analysis for streptazolin and its analogues is outlined in Scheme 1. A common structural feature of these

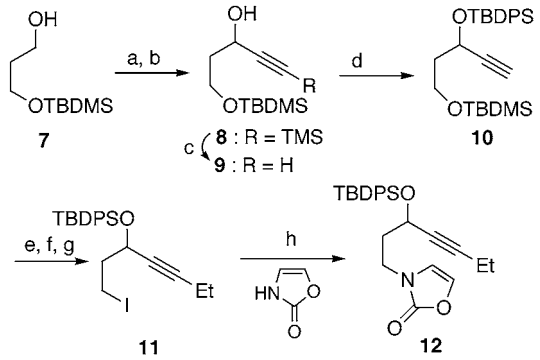
Scheme 1



natural products[3−6,9,12] is the 7-hydroxy-6-substituted-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undecan-10-one framework **3**.[8] Therefore, we envisioned that the tricyclic core framework, namely, 4-hydroxy-6-substituted-9-oxa-1-azatricyclo[6.2.1.0^{5,11}]-undec-5-en-7,10-dione **4**,[8] would be a useful intermediate for the synthesis of various streptazolin-related compounds. The tricyclic skeleton **4** might be directly constructed by the intramolecular Pauson−Khand reaction of the 2-oxazolone derivative **5**, which has a pentynyl moiety on a nitrogen atom. To the best of our knowledge, no previous reports have dealt with 2-oxazolone derivatives as an olefin counterpart in the Pauson−Khand reaction. Thus, this would be the first example in which 2-oxazolone is used as an olefin moiety (an enamine equivalent[13]) in the Pauson−Khand reaction. 2-Oxazolone-alkyne derivative **5** can be prepared from the coupling reaction between the iodo derivative **6** and 2-oxazolone. This Letter describes our preliminary results regarding (i) the stereoselective construction of the 9-oxa-1-azatricyclo[6.2.1.0^{5,11}]undec-5-en-7,10-dione skeleton based on the intramolecular Pauson−Khand reaction of 2-oxazolone derivatives and (ii) its successful application to the first total synthesis of (±)-8α-hydroxystreptazolone (**2**).

Since the targeted streptazolin-related natural products have a C_2-unit at the C_6-position,[8] we prepared the 2-oxazolone-alkyne derivative **12** with the simplest C_2-unit, an ethyl group, at the C_6-position[8] to not only identify suitable ring-closing conditions but also determine the level of stereoselectivity that could be expected in the intramolecular Pauson−Khand reaction. Thus, the 2-oxazolone-alkyne derivative **12**, required for the intramolecular Pauson−Khand reaction consistent with our retrosynthesis, was easily prepared from the known alcohol **7** by conventional means, as shown in Scheme 2. Oxidation of **7** was followed by addition

Scheme 2[a]



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

of the acetylide, derived from trimethylsilylacetylene, to afford **8** in 75% yield. The terminal silyl group of **8** was removed by base treatment to afford **9** (97%), the secondary hydroxy group of which was then protected with a *tert*-butyldiphenylsilyl (TBDPS) group to give **10** in 98% yield. Introduction of an ethyl group at the triple-bond terminus of **10** was followed by desilylation and iodination to give the iodo derivative **11** in 69% overall yield. The coupling reaction between **11** and 2-oxazolone proceeded, upon treatment with NaH in DMF, to produce **12** in 86% yield.

The intramolecular Pauson−Khand reaction of **12** was carried out under various conditions, and typical results are summarized in Table 1. Treatment of **12** with $Co_2(CO)_8$ in Et_2O gave the corresponding cobalt complex, which was then heated in acetonitrile[14] without a promoter to give only a trace amount of **13** (entry 1). Amine oxides such as trimethylamine *N*-oxide (TMANO)[15] and *N*-methylmorpholine *N*-oxide (NMO)[16] were found to be effective promoters for the Pauson−Khand reaction of cobalt-complexed **12** (entries 2−5). In particular, Pérez-Castells' procedure[17] using TMANO and 4 Å molecular sieves in toluene at −10 °C

(10) (a) Mukai, C.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *Tetrahedron Lett*. **1995**, *36*, 5761. (b) Mukai, C.; Kim, J. S.; Uchiyama, M.; Sakamoto, S. Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2903. (c) Mukai, C.; Kim, J. S.; Uchiyama, M.; Hanaoka, M. *Tetrahedron Lett*. **1998**, *39*, 7909. (d) Mukai, C.; Kim, J. S.; Sonobe, H.; Hanaoka, M. *J. Org. Chem*. **1999**, *64*, 6822. (e) Mukai, C.; Sonobe, H.; Kim, J. S.; Hanaoka, M. *J. Org. Chem*. **2000**, *65*, 6654. (f) Mukai, C.; Nomura, I.; Yamanishi, K.; Hanaoka, M. *Org. Lett*. **2002**, *4*, 1755.

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

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

(13) Very recently, the carbamate and amide functionalities were used as an enamine equivalent in 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.

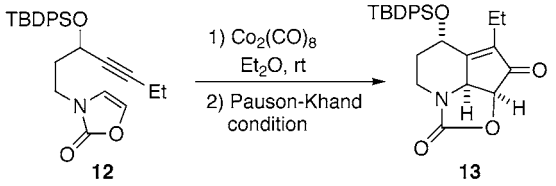
(14) (a) Hoye, T. R.; Suriano, J. A. *J. Org. Chem*. **1993**, *58*, 1659. (b) Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220.

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

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

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

Table 1. Pauson−Khand Reaction of **12**

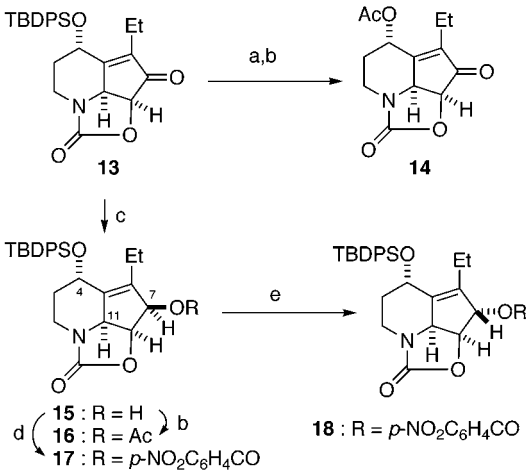


entry	promoter	solvent	time	temp.	yield (%)
1	heat	MeCN	75 min	75 °C	trace
2	TMANO·$2H_2O$	CH_2Cl_2	3 h	rt	37
3	TMANO·$2H_2O$	CH_2Cl_2	5.5 h	reflux	55
4	NMO	CH_2Cl_2	20 h	rt	38
5	TMANO/4 Å MS	toluene	12 h	−10 °C	60
6	^{i}PrSMe	$Cl(CH_2)_2Cl$	45 min	reflux	16
7	$CyNH_2$	$Cl(CH_2)_2Cl$	30 min	reflux	11

effected ring-closure of the cobalt-complexed **12**, resulting in the exclusive formation of **13** in 60% yield (entry 5). The desired product **13** was also obtained, but in lower yields, under Sugihara conditions[18] (entries 6 and7).

Desilylation of **13** followed by acetylation gave **14** in 79% yield. The relative stereochemistry of the three chiral carbon centers in **13** and **14** was determined by an examination of the NMR spectrum[19] of **14**. We next sought to transform

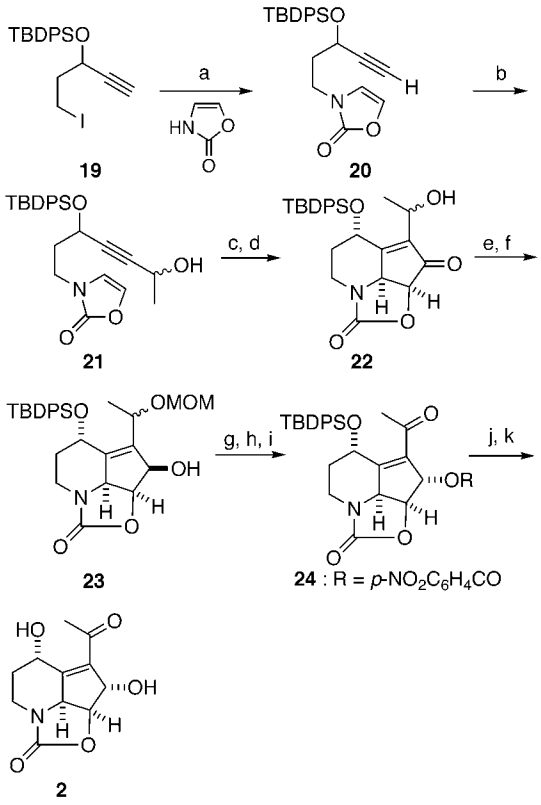
Scheme 3[a]



[a] Reaction conditions: (a) TBAF, THF, rt; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, **14** (79% from **13**), **16** (quantitative from **13**); (c) $NaBH_4$, $CeCl_3$, MeOH, 0 °C; (d) *p*-$NO_2C_6H_4COCl$, Et_3N, DMAP, CH_2Cl_2, 40 °C (95% from **13**); (e) *p*-$NO_2C_6H_4CO_2H$, DEAD, PPh_3, benzene, rt (94% from **13**).

the carbonyl functionality of **13** into a hydroxy group with the desired stereochemistry. Thus, reduction of **13** with $NaBH_4$ in the presence of $CeCl_3$ gave the alcohol **15**, which was acetylated under conventional conditions to give **16** in quantitative yield. NOE experiments[20] of **16** clearly showed 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 **15** to Mitsunobu conditions (*p*-nitrobenzoic acid, DEAD, and triphenylphosphine), which lead to the exclusive formation of **18** with the desired stereochemistry in 94% yield from **13**. *p*-Nitrobenzoylation of **15** gave **17**, the C_7-epimer of **18**, in 95% overall yield from **13**. Comparison of the coupling constant[21] between H-7 and H-8 in both **17** and **18** with those of streptazolin and its related compounds, in combination with the results of NOE experiments[20] of **16**, unambiguously established that both **17** and **18** have the stereochemistries depicted in Scheme 3.

Scheme 4[a]



[a] Reaction conditions: (a) NaH, DMF, 0 °C, (83%); (b) NaHMDS, MeCHO, THF, −78 °C (86%); (c) $Co_2(CO)_8$, Et_2O, rt; (d) TMANO, 4 Å MS, toluene, −10 °C (51%); (e) MOMCl, $^i Pr_2NEt$, CH_2Cl_2, reflux; (f) $NaBH_4$, $CeCl_3$, MeOH, 0 °C (90%); (g) *p*-$NO_2C_6H_4CO_2H$, PPh_3, DEAD, benzene, 60 °C; (h) concentrated HCl, THF, 60 °C; (i) Dess−Martin periodinane, CH_2Cl_2, rt (65%); (j) K_2CO_3, MeOH, rt; (k) TBAF, THF, rt (82%).

We could now develop an efficient procedure for constructing the tricyclic framework of streptazolin and its related

(18) 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.

(19) In a NOE experiment with **14**, no enhancement was observed between H-4 and H-11, while the methylene protons of the ethyl group were enhanced by 4.2% upon irradiation at H-4.

(20) In a NOE experiment with **16**, irradiation of H-8 produced not only 11.4% enhancement of H-7 but also 12.6% enhancement of H-11.

(21) H-7 of **17** appeared at δ 5.89 as a doublet with $J = 4.9$ Hz, while that of **18** resonated at δ 5.80 as a singlet. The smaller coupling constant ($J = 0$ Hz) is in good agreement with that of streptazolin and streptazolin acetate ($J = 0$ Hz).[1,5]

natural products, in which all of the stereogenic centers of 8α-hydroxystreptazolone (**2**) are constructed in a stereocontrolled fashion. Therefore, we next focused on the first total synthesis of 8α-hydroxystreptazolone (**2**). The coupling reaction of the iodo derivative **19**[22] with 2-oxazolone afforded **20** in 83% yield. Treatment of **20** with acetaldehyde in the presence of NaHMDS gave **21** in 86% yield as a mixture of two diastereoisomers. Cobalt complexation of **21**[23] was followed by the Pauson−Khand reaction under the Pérez-Castells' conditions[17] (TMANO and 4 Å molecular sieves in toluene at −10 °C) to afford the tricyclic compound **22** in 51% yield. The secondary hydroxy group of **22**[22] was protected with the MOM group, and the resulting compound was reduced with $NaBH_4$ in the presence of $CeCl_3$ to give **23** in 90% yield. Transformation of **23**[23] into **24** was realized in 65% overall yield upon consecutive exposure of **23** to Mitsunobu conditions, demethoxymethylation, and oxidation. Finally, this total synthesis was completed by removing two protecting groups from the secondary hydroxy moieties of **24** to give (±)-8α-hydroxystreptazolone (**2**) in 82% yield. The synthetic racemic 8α-hydroxystreptazolone (**2**) was identical to the natural compound on the basis of their ^1H and ^{13}C NMR spectra.

(22) Compound **19** was prepared from **10** in 99% yield according to the procedure described for converting **10** into **11**.

(23) Used as a mixture of two diastereoisomers.

Thus, 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-en-7,10-dione (e.g., **13** and **22**) by the intramolecular Pauson−Khand reaction of 2-oxazolone species with the proper alkyne appendages. In addition, by taking advantage of this new method, we achieved the first total synthesis of (±)-8α-hydroxystreptazolone (**2**) in a highly stereoselective manner. Since the tricyclic compound **22** 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 **22** into other related natural products are now in progress.

Acknowledgment. The authors 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 natural 8α-hydroxystreptazolone.

Supporting Information Available: Experimental procedures for conversion of **19** to **2** and spectral data and ^1H and ^{13}C NMR spectra for **2**, **13**, **14**, **22**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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