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Enantiocontrolled Construction of Tricyclic Furan Derivatives via an Asymmetric Diels–Alder Reaction

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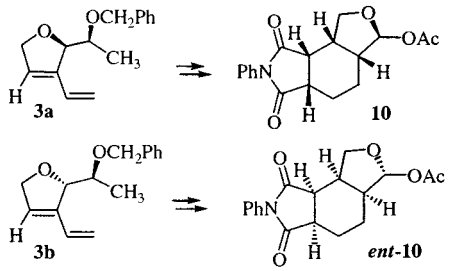
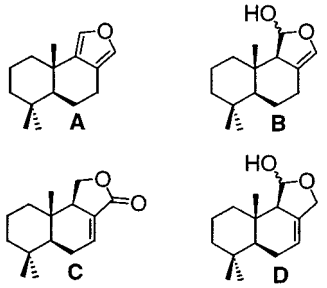
ABSTRACT



The two enantiomers of trycyclic furan derivatives were prepared respectively from Diels–Alder reactions of oxycyclic dienes 3a and 3b, followed by degradation of the 2-(benzyloxy)ethyl group. Compounds 3a and 3b can be selectively synthesized by [3+2]-cycloaddition of vinylpropargyltungsten complex with (2*S*)-(benzyloxy)-propanal.

Tricyclic furan derivatives are often found in naturally occurring compounds.[1,2] Shown in Scheme 1 are compounds

Scheme 1



A−**D**, which represent families of drimane sesquiterpenes isolated from different marine sources.[1,2] These natural oxygen heterocycles have attracted considerable synthetic attention; many of them involve semi- or racemic syntheses.[3] In this study we report the syntheses and Diels−Alder reactions[4] of chiral oxacyclic dienes **3a** and **3b** which are useful building blocks for enantiopure tricyclic furans. The 2-(benzyloxy)ethyl group remaining after the cycloaddition can be transformed into an acetate group efficiently (vide infra).

We previously reported a facile [3+2]-cycloaddition of propargyltungsten compounds with aldehydes to yield tung-

(1) (a) Appel, H. H.; Bond, R. P. M.; Overton, K. H. *Tetrahedon*. **1963**, *19*. 635. (b) Okuda, R. K.; Scheuer P. J. *J. Org. Chem*. **1983**, *48*, 1866. (c) Butler, M. S.; Capon, R. J. *Aust. J. Chem*. **1993**, *46*, 1255.

(2) (a) Jansen, B. J. M.; Groot, Ae. De *Nat. Prod. Rep*. **1991**, *8*. 309. (b) Pascual, T. J.; Urones, J. G.; Marcos, I. S.; Diez, D.; Monje, V. A. *Phytochemistry* **1986**, *25*, 711.

(3) (a) Urones, J. G.; Marcos, I. S.; Belen, G.-P.; Lithgow, A. M.; Diez, D.; Basabe, P.; Gomez, P. M. *Tetrahedron Lett*. **1994**, *35*, 3781. (b) Kanematsu, K.; Soejima, S. *Heterocycles* **1991**, *32*, 1483. (c) Ley, S. V.; Mahon, M. *Tetrahedron Lett*. **1981**, *22*, 4747. (d) Baba, Y.; Sakamoto, T.; Soijima, S.; Kanematsu, K. *Tetrahedron* **1994**, *50*, 5645. (e) Nakano, T.; Maillo, M. A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2137. (f) Howell, S. C.; Ley, S. V.; Mahon, M. *J. Chem. Soc., Chem. Commun*. **1981**, 507. (g) Barrero, A. F.; Alvarez-Manzanefa, E.; Altarejos, J.; Salido, S.; Ramos, J. M. *Tetrahedron Lett*. **1994**, *35*, 2945. (h) Hueso-Rodriguez, J. A.; Rodriguez, B. *Tetrahedron Lett*. **1989**, *30*, 859. (I) Jalani-Naini, M.; Guillerm, D.; Lallemand, J.-Y. *Tetrahedron* **1983**, *39*, 749.

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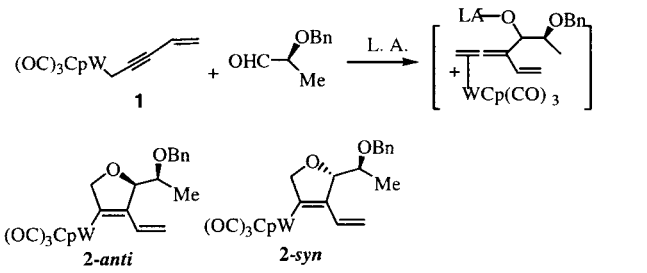
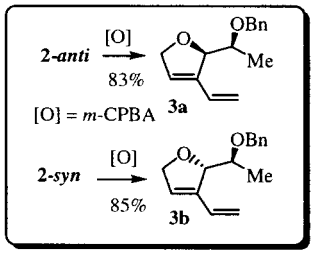
sten-2,5-dihydrofur-3-yl complexes.[5] The reaction is proposed to involve a zwitterionic intermediate. To highlight the utility of this cyclization, we prepared (*2S*)-2-(benzyloxy)propanal (ee = 98%) according to literature reports.[6] Cycloaddition of this chiral aldehyde with vinylpropargyltungsten complex **1** proceeded smoothly in the presence of Lewis acid to give a mixture of two diastereomeric products **2**-*syn*/**2**-*anti*. These two products were separable by column chromatography and the isolated yields are summarized in Scheme 2. $TiCl_4$ and $SnCl_4$ lead to *syn*-selectivity via metal

Scheme 2



L. A.	products	
$SnCl_4$	**2**-*anti*	15 %
	2-*syn*	51 %
$TiCl_4$	**2**-*anti*	14 %
	2-*syn*	69 %
BF_3·Et_2O	**2**-*anti*	60 %
	2-*syn*	14 %



chelation[7] of the aldehyde and benzyloxy group whereas BF_3·Et_2O results in the *anti*-selectivity following a Felkin−Ann model. The configurations of **2**-*anti* and **2**-*syn* were confirmed by X-ray diffraction studies of their Diels−Alder cycloadducts. Vigorous efforts were made for hydrodemetalation of **2a**-*syn* and **2**-*anti* to obtain the desired oxacyclic dienes **3a** and **3b**. We found that *m*-CPBA oxidation of **2a**-*anti* and **2a**-*syn* in CH_2Cl_2 effected hydrodemetalation to afford **3a** and **3b** in 83% and 85% yields, respectively. No other byproducts were found according to the ^{1}H NMR spectra of the crude products. In our synthetic protocol, the 2-(benzyloxy)ethyl substituent of **3a** and **3b** is the degradable group for subsequent Diels−Alder reaction.

We first examined the cycloaddition of oxacyclic diene **3a** with cyclohexenone in hot toluene (Table 1, entry 1). Three stereoisomers ca. 10:3:1 were obtained in a combined yield of 86%. Fractional crystallization of this mixture gave

Table 1. Asymmetric Diels−Alder Reaction of 3a and 3b with Dienophiles[a]

entry	reactants	conditions	products
1	**3a**	**A** (48 h)	**4a** (63%)
2	**3a**	**A** (8 h)	**5a** (72%)
3	**3a**	**A** (48 h)	**6a** (67%)
4	**3a**	**B** (3 h)	**7a** (92%)
5	**3a**	**B** (3 h)	**8a** (6:1, 94%) 67%
6	**3b**	**A** (48 h)	**4b** (69%)
7	**3b**	**A** (8 h)	**5b** (76%)
8	**3b**	**A** (48 h)	**6b** (64%)
9	**3b**	**B** (3 h)	**7b** (93%)
10	**3b**	**B** (3 h)	**8b** (13:1, 96%) 86%

[a] Condition **A**: BF_3·Et_2O (1.0 equiv), 23 °C, CH_2Cl_2 −78 °C to 23 °C. Condition **B**: toluene, 80 °C.

the major diastereomer **4a** in only 23% yield. This problem can be circumvented with the use of BF_3·Et_2O which effected the cycloaddition at 23 °C, yielding a single diastereomer **4a** in 63% yield after recrystallization. The configuration of **4a** was determined by ^{1}H NOE spectroscopy summarized in Scheme 3. The regiochemistry is inferred from the H^3 proton (δ 3.12), which shows a quartet (dd, J = 10.0, 8.2 Hz), whereas the H^4 proton (δ 1.84) shows a complex multiplet. The structure of **4a** indicates that cyclohexenone

(5) (a) Wang, S.-H.; Shiu, L.-H.; Liao, Y.-L.; Wang, S.-L.; Lee, G.-H.; Peng, S. M.; Liu R.-S. *J. Am. Chem. Soc.* **1996**, *118*, 530. (b) Shieh, S.-J.; Tang, T.-C.: Lee, J.-S., Lee, G.-H., Peng, S.-M.; Liu, R.-S. *J. Org. Chem.* **1996**, *61*, 3245.

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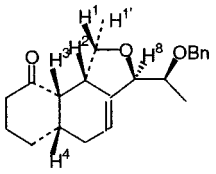
(7) (a) Burke, S. D.; Deaton, D. N.; Olsen, R. J.; Armistead, D. M.; Blough B. E. *Tetrahedron Lett.* **1987**, *28*, 3905. (b) Comins, D. L.; Herrick, J. J. *Tetrahedron Lett.* **1983**, *48*, 2775.

Scheme 3



Irradiation	Intensities
H^3 (δ 3.13)	H^2 (3.12 %)
	H^4 (δ1.84, 7.39 %)
H^2 (δ 2.85)	H^3 (2.8 %), H^1 (5.6%)
	$H^{1'}$ (0 %),
H^8 (δ 4.23)	H^1 (0 %), $H^{1'}$(2.0 %)

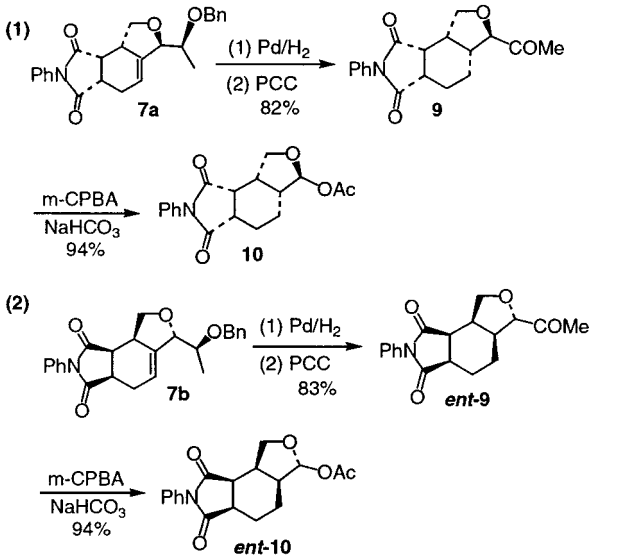
approaches the diene **3a** in an *endo* fashion but opposite to the (benzyloxy)ethyl substituent. This stereoselectivity is remarkable since eight isomers are likely to occur. $BF_3{\cdot}Et_2O$ also effected asymmetric cycloaddition of **3a** with benzoquinone and cyclopentenone (CH_2Cl_2, 23 °C) to afford compounds **5a** and **6a** in 72% and 67% yields, respectively, after a single crystallization (entries 2−3). The reaction of **3a** with *N*-phenylmaleimide and maleic anhydride proceeded smoothly in hot toluene (80 °C, 3 h), yielding **7a** and **8a** exclusively. In entry 5, the products consist of a 6:1 diastereomeric mixture, finally affording pure **8a** in 67% yield after crystallization.

Shown in Table 1 are the results of asymmetric Diels−Alder reactions of the oxacyclic diene **3b** with the same olefins. Using the same approach, the cycloadducts **4b**−**8b** were obtained as one diastereomer (64−93% yields) after purification by recrystallization. These results indicate that the (benzyloxy)ethyl substituent of **3b** is equally effective as that of **3a** in the asymmetric cycloadditions. In entry 10, the maleic adduct is a 13:1 diastereomeric mixture (96% combined yields). Crystallization of this mixture gave pure anhydride **8b** in 86% yield. Determination of the stereochemistry relies on ^{1}H NOE effect as well as X-ray diffraction studies of **5b** and **8b**.[8,9] Again, the observed stereoselectivities were attributed to the *endo*-facial cycloaddition and the steric effect of the 2-(benzyloxy)ethyl substituent.

Notably, compounds **4a**−**8a** are envisaged to be the enantiomers of **4b**−**8b** if the 2-(benzyloxy)ethyl substituent is ignored. It is imperative to remove this substituent with cleavage of the tethered C−C bond to yield a simple furan derivative. An efficient and stereospecific method has been developed and the protocol is illustrated in Scheme 4.

The benzyl group of compound **7a** was removed by Pd/H_2 which also resulted in the stereoselective hydrogenation of the internal olefin to give the alcohol (Scheme 4). Subsequent oxidation of this crude alcohol with PCC

Scheme 4



afforded the ketone **9** in 82% overall yield. The molecular structure of **9**[10] was determined by an X-ray diffraction study which reveals that **9** has two *cis*-configurations in the three fused rings. Degradation of the acetyl group follows recent work by Kusumoto[11] who reported the alkoxyalkyl group is more prone to migration than an alkyl group in Baeyer−Villager oxidations. *m*-CPBA oxidation of compound **9** gave the tricyclic lactol **10** in 94% yield. This transformation was shown to proceed exclusively via retention of stereochemistry. Similarly, we also used compound **7b** to obtain the enantiomers of compounds **9** and **10** in good yields. following the same protocol. The [α] values of the resulting products *ent*-**9** ([α] = +19.2, c 4.22, $CHCl_3$) and *ent*-**10** ([α] = −71.3, c 1.68, $CHCl_3$) match well with those of **9** ([α] = +19.1, c 1.64, $CHCl_3$) and **10** ([α] = +71.3, c 1.02, $CHCl_3$), respectively. HPLC analyses show that ee values of **9** and *ent*-**9** were 98% and 97%, respectively. The structure of *ent*-**9** was also confirmed by an X-ray study.[12]

In summary, we used tungsten-mediated [3+2]-cycloaddition for selective syntheses of enantiopure oxacyclic dienes **3a** and **3b**. The 2-(benzyloxy)ethyl substituent of **3a** and **3b** effected asymmetric Diels−Alder reaction; the cycloadducts derived from benzoquinone, cyclohexenone, cyclopentenone, *N*-phenylmaleimide, and maleic anhydride were obtained as a single diastereomers in 63−93% yields. We have also developed an efficient method for transformation of the 2-(benzyloxy)ethyl substituent into an acetate group. Using this method, the two enantiomers of tricyclic furan derivatives **10** and *ent*-**10** were obtained separately with high

(8) Crystal data for **5b**: monoclinic space group, *P*2(1), a = 11.3392 (18) Å, b = 6.4915(11) Å, c = 12.206 Å, V = 897.4(3) Å^3, Z = 2, R1 = 0.0607 and wR2 = 0.1506 for 3514 unique reflections > 2 σ(I).

(9) Crystal data for **8b**: orthorhombic space group, $P2_12_12_1$, a = 6.8329 (2) Å, b = 8.1545(2) Å, c = 29.8514 Å, V = 1663.29 Å^3, Z = 4, R1 = 0.0749 and wR2 = 0.1057 for 3320 unique reflections > 2 σ(I).

(10) Crystal data for **9**: orthorhombic space group, $P2_12_12_1$, a = 9.2239-(19) Å, b = 26.248(6) Å, c = 6.4941(13) Å, z = 4, V = 1572.3(6) Å^3, R1 = 0.0441 and wR2 = 0.1064 for 3506 unique reflections > 2 σ(I).

(11) Matsutani, H.; Ichikawa, S.; Yaruva, J.; Kusumoto, T.; Hiyama, T. *J. Am. Chem. Soc*. **1997**, *119*. 4541.

(12) Crystal data for *ent*-**9**: orthorhombic space group, $P2_12_12_1$, a = 6.4935 (11) Å b = 9.2208 (19) Å, b = 26.244(4) Å, z = 4, V = 1571.4 (6) Å^3, R1 = 0.0447 and wR2 = 0.1019 for 3551 unique reflections > 2 σ(I).

enantiopurity. The success of this example highlights the use of oxacyclic dienes **3a** and **3b** for facile syntheses of enantiopure forms of tricyclic furan frameworks.

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Supporting Information Available: Experimental procedures and spectral data of new compounds. Crystal data of compounds **5b**, **8b**, **9**, and *ent*-**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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