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Total Syntheses of Yingzhaosu A and of Its C(14)-Epimer Including the First Evaluation of Their Antimalarial and Cytotoxic Activities

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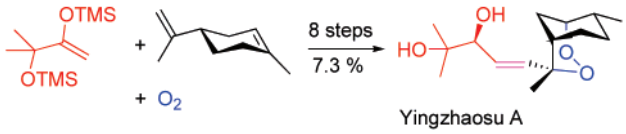

The molecular structure of the naturally occurring antimalarial agent yingzhaosu A (**1**) is characterized by a 2,3-dioxabicyclo[3.3.1]nonane system (**3a**), an allylic alcohol, a homoallylic alcohol, and five stereogenic centers. Herein we report on the total synthesis of yingzhaosu A (**1**) in eight steps and 7.3% overall yield starting from (*S*)-limonene (**12**). To maximize efficacy, the bridged bicyclic endoperoxide molecular core was constructed by a multicomponent free-radical domino reaction in which five bonds are formed in a single operation. In addition, reaction protocols that are compatible with the sensitivity of the peroxide function to strong basic and nucleophilic reagents as well as to reducing agents were employed. An intriguing step involved the selective hydrogenation of a carbon−carbon double bond in the presence of a peroxide and an aldehyde function to give aldehyde peroxide **7**. The two major synthons (aldehydoperoxide **7** and its complementary five-carbon atom unit **35**) were linked through a Mukaiyama aldol reaction followed by in situ dehydration under mild buffered basic conditions. The carbonyl group in the resulting peroxidic enone **39** was stereoselectively reduced with either *R*-CBS catalyst (**42b**) to give, after in situ desilylation, yingzhaosu A (**1**) or with *S*-CBS catalyst (**42a**) its C(14)-epimer **40**. The first quantitative in vitro and in vivo data for the antimalarial activity of yingzhaosu A (**1**) and its C(14)-epimer **40** are reported. The C(14)-epiyingzhaosu A (**40**) exhibits potent cytotoxic activity against the KB nasal-pharyngeal cancer cell line in vitro.

Introduction

Bridged-bicyclic peroxide yingzhaosu A (**1**) was isolated from an extract of *Artabotrys uncinatus* (Annonaceae) that was used in China as a traditional remedy for treatment of malaria.[1] Following isolation and structure determination, molecular structure **1** was corroborated through total synthesis and X-ray diffraction analysis of the carbonate derivative of the synthetic product.[2] Although yingzhaosu A was repeatedly reported to be the antimalarial constituent of the above-mentioned herbal medicament, no quantitative assessment of its potency has ever been reported.[3] Furthermore, following an abortive attempt to repeat its isolation from the plant,[4] it was questioned whether yingzhaosu A is a genuine constituent of the living plant or an artifact.[5] Contemporaneously, the study of tetracyclic trioxane artemisinin (qinghaosu) (**2**), originating from a different Chinese traditional herbal remedy,[6] and many of its synthetic and semisynthetic derivatives led to the development of the

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(1) Liang, X. T.; Yu, D. Q.; Wu, W. L.; Deng, H. C. *Acta Chim. Sin.* **1979**, *37*, 215−230.

(2) (a) Xu, X. X.; Zhu, J.; Huang, D.-Z.; Zhou, W.-S. *Tetrahedron Lett.* **1991**, *32*, 5785−5788. (b) Zhou, W. S.; Xu, X. X. *Acc. Chem. Res.* **1994**, *27*, 211−216.

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(5) (a) Jefford, C. W. In *Advances in Drug Research. Vol.29: Peroxidic Antimalarials*; Jefford, C. W., Ed.; Academic Press: 1997; pp 270−325. (b) Jefford, C. W. *Curr. Med. Chem.* **2001**, *8*, 1803−1826.

(6) Lin, M.-Y.; Ni, J.-M.; Fan, J. F.; Tu, Y.-Y.; Wu, Z.-H.; Wu Y.-L.; Chou, W.-S. *Acta Chim. Sin.* **1979**, *37*, 129−141.

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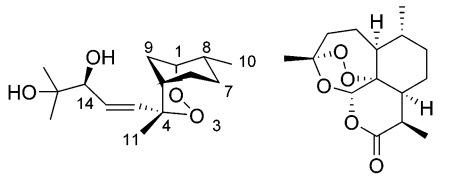
first-generation antimalarial peroxide drugs.[7] On a parallel course a variety of endoperoxides containing the molecular core of yingzhaosu A (**1**), namely a 2,3-dioxabicyclo[3.3.1]nonane system **3**, as putative pharmacophore were synthesized.[8−13] While some of these synthetic peroxides, e.g., **4**,[9a] were found to be highly potent and nontoxic antimalarial drug candidates,[8,9] the enigma concerning the potential antimalarial value of yingzhaosu A (**1**) itself remained. The first total synthesis of yingzhaosu A (**1**) by Xu et al.[2a] was based on a stimulating strategy but involved a laborious 15-step sequence that could not be efficaciously applicable on preparative scale. Yields in several steps of the synthesis of **1** were not reported,[2a] but an estimation of the overall yield leads to a figure well below 1%. The preparation of an endoperoxide key intermediate, used in another synthesis, was outlined in a recent review.[14]



Driven by the challenge of constructing this intriguing molecule and by the desire of supplying yingzhaosu A (**1**) on a scale that would allow the evaluation of its antimalarial activity and other biological properties, we developed the total synthesis described herein. This methodology allows the efficient eight-step syntheses of yingzhaosu A (**1**) and of its C(14)-epimer **40** on a preparative scale.[15] We also present, for the first time, data about their antimalarial activity as well as preliminary information about their cytotoxic properties.

Synthesis

Retrosynthetic paths a and b outlined in Scheme 1 were considered at the outset of this work. Path a is based on the two chiral synthons **6** and **7**, which together contain all the stereogenic centers comprised in the target molecule **1** and its immediate precursor **5**, in the correct absolute configuration. Retrosynthetic path b is based on the same aldehyde **7**, but its complementary synthon **10**, or its synthetic equivalent **11**, are achiral thus forcing the postponement of the consolidation of one of the five stereogenic centers to the end of the synthesis. The use of aldehyde **7** as key intermediate was introduced by Xu et al.; however, their synthesis of **7** was based on an 11-step low-yielding process.[2a] As starting material for aldehyde **7** we chose β-sulfenyl endoperoxide **8**. Compound **8** is readily prepared on a multigram scale from *S*-limonene (**12**) by a methodology recently developed in our laboratory.[10] It was originally used as an intermediate for the preparation of a class of antimalarial β-sulfonyl endoperoxides[9] represented here by drug candidate **4**.[9a] As summarized in Scheme 2, the 2,3-dioxabicyclo-[3.3.1]nonane system (**3a**) in endoperoxide−hydroperoxides **13** and **14** is constructed in a multicomponent domino free-radical reaction in which five new bonds are formed in one operation. The resulting hydroperoxy group is reduced in the same vessel to give the β-sulfenyl endoperoxide **8** and its diastereomer **15** (50% combined yield, **8**:**15** = 55:45).[10a,16] Due to difficulties encountered on attempted chromatographic separation of **8** and **15**, separation of the diastereomers was postponed to a subsequent step. Our synthetic plan required a stereoselective deoxygenation of the hydroxyl group and conversion of the phenylsulfenyl group into a tertiary formyl group via a Pummerer reaction.[17] The choice of appropriate reactions throughout this synthesis was curbed by the susceptibility of the peroxide system to reducing agents as well as to strong nucleophiles and bases.[18,19]

(7) For some recent reviews, see: (a) Posner, G. H.; O'Neill, P. M. *Acc. Chem. Res.* **2004**, *37*, 397−404. (b) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 2945−2964. (c) Tang, Y.; Dong, Y.; Vennerstrom J. L. *Med. Res. Rev.* **2004**, *24*, 425−448. (d) Jung, M.; Lee, K.; Kim, H.; Park, M. *Curr. Med. Chem.* **2004**, *11*, 1265−1284. (e) Bez, G.; Kalita, B.; Sarmah, P.; Barua, N. C.; Dutta, D. K. *Curr. Org. Chem.* **2003**, *7*, 1231−1255. (f) Robert, A.; Dechy-Cabaret, O.; Cazelles, J.; Meunier, B. *Acc. Chem. Res.* **2002**, *35*, 167−174. (g) Vroman, J. A.; Alvim-Gaston, M.; Avery, M. A. *Curr. Pharm. Des.* **1999**, *5*, 101−138. (h) Bhattacharya, A. K.; Sharma, R. P. *Heterocycles* **1999**, *51*, 1681−1745. See also ref 5.

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(9) (a) Bachi, M. D.; Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Cumming, J. N.; Plyopradith, P.; Xie, S. J.; Shapiro, T. A.; Posner, G. H. *J. Med. Chem.* **2003**, *46*, 2516−2533. (b) Bachi, M. D.; Korshin, E. E.; Ploypradith, P.; Cumming, J. N.; Xie, S. J.; Shapiro, T. A.; Posner, G. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 903−908. (c) Bachi, M. D.; Posner, G. H.; Korshin, E. E. PCT Int. Appl. WO 99/12900, 1999; *Chem. Abstr.* **1999**, *130*, 237573.

(10) (a) Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Konstantinovski, L.; Posner, G. H.; Bachi, M. D. *Tetrahedron* **2002**, *58*, 2449−2469. (b) Bachi, M. D.; Korshin, E. E. *Synlett* **1998**, 122−124.

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(12) O'Neill, P. M.; Searle, N. L.; Raynes, K. J.; Maggs, J. L.; Ward, S. A.; Storr, R. C.; Park, B. K.; Posner, G. H. *Tetrahedron Lett.* **1998**, *39*, 6065−6068.

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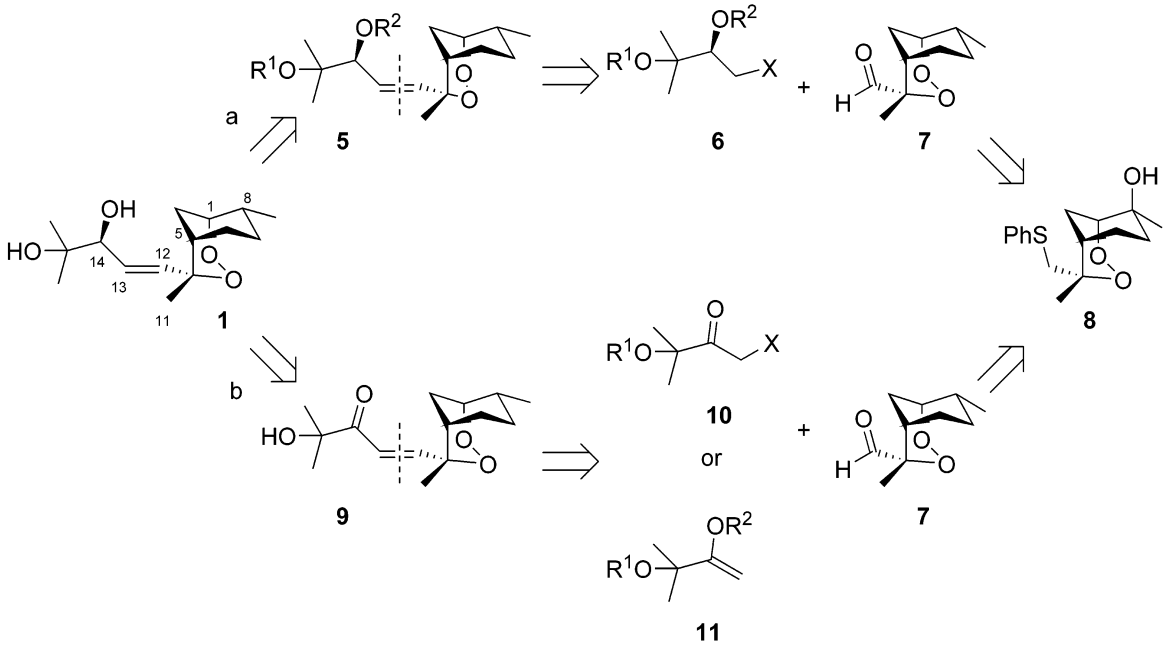
(16) For the safety precautions in working with endoperoxides, see ref 10a.

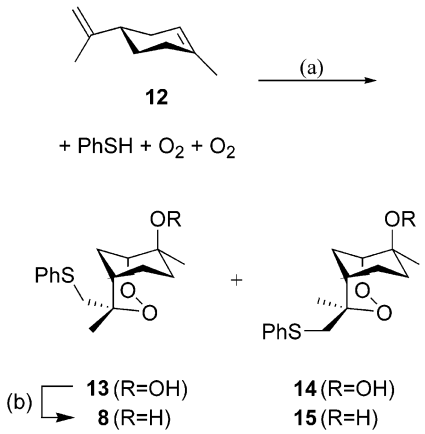
(17) For reviews on the Pummerer reaction, see: (a) De Lucchi, O.; Miotti, U.; Modena, G. *Org. React.* **1991**, *40*, 157−405. (b) Moiseenkov, A. M.; Dragan, V. A.; Veselovski, V. V. *Russ. Chem. Rev.* **1991**, *60*, 643−657.

(18) (a) Kornblum, N.; DeLamare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880−881. (b) Clennan, E. L.; Foote, C. S. In *Organic Peroxides*; Ando, W., Ed.; Wiley: Chichester, 1992; pp 255−318. (c) Saito, I.; Nittala, S. S. In *The Chemistry of Peroxides*; Patai, S., Ed.; Wiley: Chichester, 1983; pp 311−374.

SCHEME 1



SCHEME 2[10a,a]



[a] Key: (a) AIBN, *hν*, CH_3CN; (b) Ph_3P.

Removal of the hydroxyl group in **8** by dehydration followed by hydrogenation complies with such requirements.[20]

Indeed, dehydration of the mixture of sulfides **8** and **15** afforded a mixture of endocyclic alkene **16** and exocyclic alkene **17** (each as a mixture of the 4*R* and 4*S* diastereoisomers) in 93% combined yield (Scheme 3). Since previous attempts to selectively hydrogenate the olefinic function in *β*-sulfenyl peroxides similar to **16** and **17** gave poor results,[9a] this operation was postponed to a latter stage. To avoid affecting the double bond of **16** and **17**, selective *m*-CPBA oxidation of the sulfide functionality of **16a**,**b** and **17a**,**b** was performed at −40 °C. It resulted in a mixture of all the eight possible stereo- and regioisomeric sulfoxides **18a**−**d** and **19a**−**d** (Scheme 3). Except for a small sample, which was fractionated for analytical purposes,[21] the synthetic process was continued with the mixture of all isomeric sulfoxides.

Treatment of sulfoxides **18a**−**d** and **19a**−**d** with trifluoroacetic anhydride and 2,6-lutidine afforded via a Pummerer rearrangement the thiohemiacetal esters **20a**−**h** (Scheme 4). Standard hydrolysis of thiohemiacetals **20** by saturated $NaHCO_3$ solution[17] was found to be slow and inefficient. Acidic hydrolysis[22] of the thiohemiacetal ester function of **20** on silica, by transacetalization to glyoxalic acid impregnated on silica gel,[23] as well as sulfur extrusion by mercury[24a−c] or copper salts,[24d] resulted in the formation of sulfur containing byproducts and low to moderate yields of crude unsaturated aldehydes **21**−**24**. However, hydrolysis of crude **20a**−**h** at −10 °C, under the mild basic conditions provided by 1 equiv of morpholine in methanol/dichloromethane,[25] afforded a mixture of the four isomeric aldehydes **21**−**24** in high yield. Under these conditions the adverse base-catalyzed destruction of the peroxide functionality through a Kornblum rearrangement was prevented.[18,19]

The mixture of aldehydes **21**−**24** was separated by flash chromatography to afford a fraction containing two regioisomeric olefinic aldehydes **21** and **22** possessing the desired 4*S* chirality and another fraction containing the two regioisomers **23** and **24** having 4*R* configuration

(19) Szpilman, A. M.; Korshin, E. E.; Hoos, R.; Posner, G. H.; Bachi, M. D. *J. Org. Chem.* **2001**, *66*, 6531−6540.

(20) Attempts to convert the tertiary hydroxyl at C(8) into various thionocarbonates, thionocarbamates or oxalyl thiohydroxamates for further application of the Barton-McCombie free radical deoxygenation failed.

(21) See the Experimental Section.

(22) Satchell, D. N. P.; Satchell, R. S. *Chem. Soc. Rev.* **1990**, *19*, 55−81.

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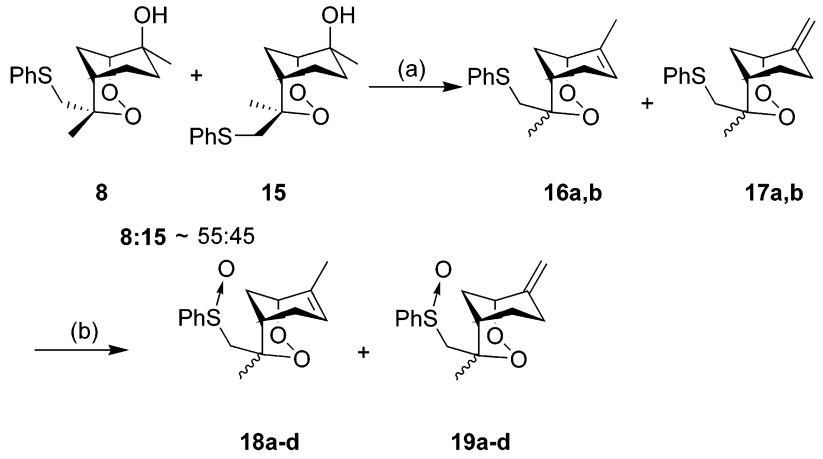
(24) (a) Corey, E. J.; Hase, T. *Tetrahedron Lett.* **1975**, 3267−3268. (b) Degani, I.; Foci, R.; Regondi, V. *Synthesis* **1981**, 51−53. (c) Soderquist, J. A.; Miranda, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 10078. (d) Cazes, B.; Julia, S. *Tetrahedron Lett.* **1978**, 4065−4068.

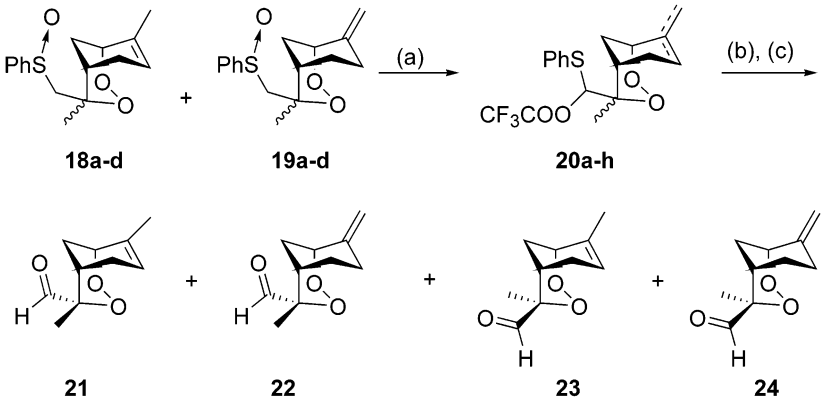
(25) Craig, D.; Daniels, K.; Mackenzie, A. R. *Tetrahedron Lett.* **1990**, *31*, 6441−6444.

SCHEME 3[a]



[a] Key: (a) 4.3 equiv of $SOCl_2$, 11 equiv of pyridine, CH_2Cl_2, 0 °C, 93% yield; (b) 1.1 equiv of *m*-CPBA, EtOAc, −40 °C, 94% yield.

SCHEME 4[a]

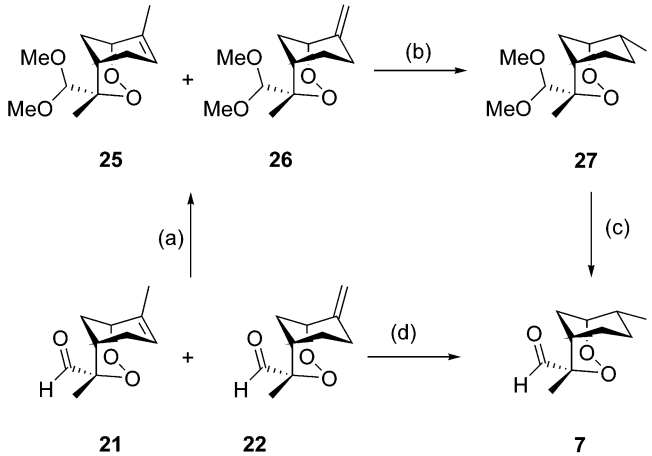


[a] Key: (a) 5 equiv of $(CF_3CO)_2O$, 10 equiv of 2,6-lutidine, CH_2Cl_2, −35 °C; (b) 1.1 equiv of morpholine, MeOH/CH_2Cl_2, −10 to 0 °C; (c) Separation by flash chromatography. Yields (two steps): **21** + **22**; 43% (ratio: 83:17), **23** + **24**; 30% (ratio: 83:17).

(Scheme 4). Configuration at C(4) was determined using empirical rules established for configurational assignment of geminal substituents on the C(4) stereogenic center of other 2,3-dioxabicyclo[3.3.1]nonane derivatives.[10a] It is based on a significant difference in the chemical shifts of the C(11) methyl group in the ^{1}H NMR spectra of epimer **21** versus that of **23** and of epimer **22** versus that of **24**, deriving from higher deshielding effects by the O(2) atom on its *syn* methyl groups in **23** and **24** as compared to the *anti* methyl group in **21** and **22**. Thus, the C(11)H_3 signal of **23** is seen at 1.56 while that of its C(4)-epimer **21** is observed at 1.07. Likewise, the C(11)-H_3 signal of **24** is detected at 1.44 while that of its 4*S*-epimer **22** appears at 1.17.

In our first version of the total synthesis of yingzhaosu A (**1**),[15] the aldehyde functionality of **21** and **22** was protected as the dimethyl acetal using acid catalyst Amberlyst-15 in neat trimethyl orthoformate (Scheme 5).[26] Chemoselective platinum oxide-catalyzed hydrogenation of the double bonds in the resulting acetals **25** and **26** occurs at temperatures below −5 °C without affecting the peroxide functionality. Hydrogenation of both *exo*- and *endo*-cyclic double bonds occurs stereoselectively

SCHEME 5[a]

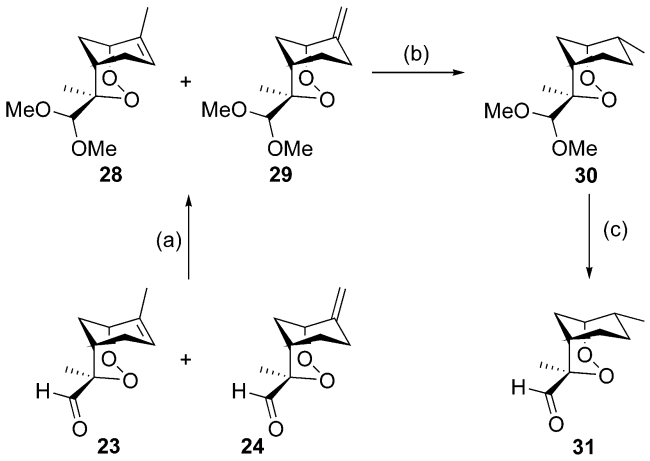


[a] Key: (a) Amberlyst-15, neat $HC(OMe)_3$, 94% yield; (b) H_2, 0.1 equiv of PtO_2, −10 °C, EtOAc, 84% yield; (c) 2.5 equiv of TsOH, 25 equiv of $CHOCOOH{\cdot}H_2O$, CH_2Cl_2, 93% yield; (d) H_2, 0.15 equiv of PtO_2, −11 to −12 °C, EtOAc, 90% yield.

from the convex face only to provide the desired saturated acetal **27** as a single diastereoisomer in good yield.

(26) Patwardhan, S. A.; Dev, S. *Synthesis* **1974**, 348−349.

SCHEME 6[a]



[a] Key: (a) Amberlyst-15, neat $HC(OMe)_3$, 93% yield; (b) H_2, 0.1 equiv of PtO_2, −10 °C, EtOAc, 77% yield; (c) 2.5 equiv of TsOH, 25 equiv of $CHOCOOH{\cdot}H_2O$, CH_2Cl_2, 98% yield.

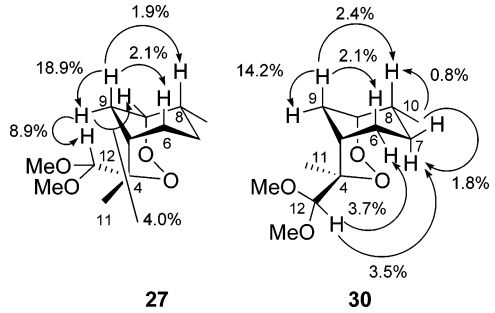


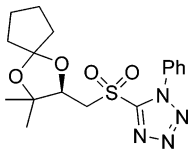
FIGURE 1. Selected NOE difference values for acetals **27** (25 °C in $CDCl_3$) and **31** (in C_6D_6).

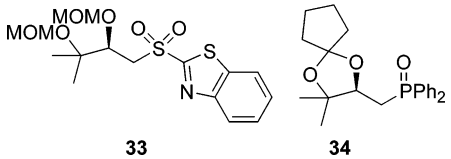
Likewise, isomeric acetals **28** and **29**, deriving from aldehydes **23** and **24**, were hydrogenated to a single saturated acetal **30** (Scheme 6).

The configuration at the newly formed stereogenic center at C(8) was determined by ^1H NOE difference experiments (Figure 1). The C(8) hydrogen atoms of **27** and **30** show a remote NOE of 1.9% and 2.4%, respectively, upon irradiation of the corresponding axial C(9) hydrogen atom, thus confirming the axial confirmation and the 8*R* configuration of this stereogenic center. The signal of the C(10)-methyl protons of **30** shows a 1.8% enhancement through interaction with the axial C(7) proton. The NOE data confirmed also the stereochemistry at C(4) independently assigned as described above. Thus, for acetal **27** a NOE response of 8.9% was observed between the C(12) acetal proton and the equatorial C(9) proton indicating that the configuration at C(4) is *S*. No such interaction is observed on in the case of acetal **30**, where the C(12) acetal hydrogen shows a NOE of 3.7% on the equatorial C(6) hydrogen and a NOE of 3.5% on the axial C(7) proton.

Deprotection of acetals **27** and **30** to afford the corresponding aldehydes **7** and **31** was performed by TsOH catalyzed transacetalization with glyoxalic acid (Schemes 5 and 6). This method takes advantage of the low solubility of TsOH, glyoxalic acid and its corresponding acetal in dichloromethane. Under these mild reaction conditions essentially pure aldehydes **7** and **31** were obtained in excellent yield by filtering off the insoluble material.

The finding that the carbon−carbon double bonds of endoperoxide acetals **25/26** and **28/29** can be chemoselectively hydrogenated at temperatures in the range of −5 to −10 °C led us to explore the direct hydrogenation of unprotected aldehydes **21** and **22**. In this instance, a systematic study revealed remarkably high temperature dependence. It was found that at temperatures above −10 °C concomitant hydrogenation of the olefinic double bond and of the aldehyde functionality took place. Hydrogenation carried out during 3 h at −13 to −14 °C revealed that while consumption of starting material was incomplete, desired aldehyde **7** (50% yield) was accompanied by a mixture of products devoid of the peroxide function. Below −14 °C the exocyclic olefinic bond of aldehyde **22** is reduced within a few minutes but the endocyclic double bond of aldehyde **21** (the major constituent) is not hydrogenated. Eventually it was found that when hydrogenation is carried out at −11 to −12 °C complete conversion of the starting material is achieved within 50 min to afford aldehyde **7** in 90% yield (Scheme 5). This hydrogenation provides a unique example of chemoselective hydrogenation of a carbon−carbon double bond in the presence of both aldehyde and peroxide functions.





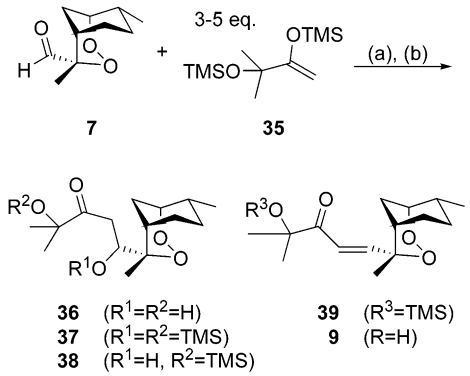
Having obtained the bicyclic peroxide synthon, the enantiomerically pure aldehyde **7**, in satisfactory overall yield, we examined the possibility of condensing it with a chiral side-chain synthon of type **6** (Scheme 1, path a). Attempts to induce a condensation of aldehyde **7** with chiral Julia−Kociensky sulfones[27] **32** and **33** as well as with Horner−Wittig reagent[28] **34** under a variety of reaction conditions failed.[29] Failures seem to derive from a combination of factors: insufficient reactivity of the sterically encumbered aldehyde function and high sensitivity of the endoperoxide function in **7** to strong bases

(27) (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856−878. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336−357. (c) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26−28.

(28) For leading general reviews on the Wittig and the related Horner−Wadsworth−Emmons phosphorus-based olefinations, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927. (b) Clayden, J.; Warren, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 241−270. (c) Vedejs, E.; Peterson, M. J. *Adv. Carbanion Chem.* **1996**, *2*, 1−85. (d) Rein, T.; Pedersen, T. *Synthesis* **2002**, 579−594. (e) Molt, O.; Schrader, T. *Synthesis* **2002**, 2633−2670. (f) Valentine, D. H., Jr.; Hillhouse, J. H. *Synthesis* **2003**, 317−334.

(29) Szpilman, A. M. Ph.D. Thesis, the Weizmann Institute of Science, Rehovot, 2003.

SCHEME 7[a]



[a] Key: (a) 3−4 equiv of $TiCl_4$, −78 °C, CH_2Cl_2, 4 h; (b) see Table 1.

and nucleophiles. At temperatures above −10 °C, both synthons are quickly destroyed while at lower temperatures no reaction occurs. While the alternative approach involving nonchiral synthons of type **10** (Scheme 1, path b) was successfully applied by Xu et al. using arsenium ylide Ph_3As =CHC(O)CMe_2OH,[2] a model experiment, performed in our laboratory, using a stabilized phosphorus ylide, namely Ph_3P =CHC(O)Ph, gave unsatisfactory results.[30,31] To avoid limitations that may derive from the base-sensitivity of endoperoxide aldehyde **7** we chose to investigate the application of the Lewis acid catalyzed Mukaiyama aldol reaction[15,32,33] for connecting a side-chain synthon of type **11** (Scheme 1, path b).

It was found that treatment of aldehyde **7** with 3 equiv of enol ether **35**[34] and 3 equiv of titanium tetrachloride at −78 °C, followed by quenching with aqueous potassium carbonate at low temperature, afforded a crude mixture of three aldol addition products **36**−**38** (Scheme 7). Acidic hydrolysis of this crude mixture afforded the single aldol addition product **36** in good yield (Table 1 entry 1). In contrast, quenching an identical reaction mixture with pyridine followed by aqueous workup afforded a moderate yield of impure α,β-unsaturated ketone **39** together with aldol addition products **37** and **38** (Table 1, entry 2). This serendipitous observation

TABLE 1. Mukaiyama Aldol Addition of TMS-enol Ether 35 to Aldehyde 7 (Step a) with in Situ Dehydration (Step b) (Scheme 7)

		yield (%)			
entry	conditions for step b	**36**	**37**	**38**	**39**
1	0.5 M K_2CO_3, 0 °C, 1 h, then HCl/MeOH	70			
2	18 equiv of pyridine, 0 °C, 10 min		15[a]	27	27[a]
3	32 equiv of pyridine, −78 to +25 °C, 2 h			22[b]	20[b]
4	23 equiv of pyridine, −40 to 0 °C, 7 h				20
5	21 equiv of pyridine, −20 to −30 °C, 11 h		13		70

[a] These products were isolated in impure state, and the yields were determined after conversion into **36** and **9**. [b] These products were not separated, and the yields are based on the ^1H NMR spectra of the mixture.

prompted us to develop a one-pot procedure for the synthesis of α,β-unsaturated ketone **9** involving aldol addition followed by in situ base-induced dehydration.[35] Such a process would be driven by the strong titanium−oxygen affinity and eventually result in the formation of the double bond through titaniumoxide dichloride extrusion. Quenching the reaction mixture with triethylamine instead of pyridine resulted in an instant decomposition of all endoperoxidic compounds. Dehydration using pyridine at temperatures above −20 °C resulted in the partial decomposition of the endoperoxidic products and afforded α,β-unsaturated ketone **39** in low yield (Table 1, entries 3 and 4). No dehydration could be observed at temperatures below −40 °C. Eventually, the aldol addition was carried out by stirring aldehyde **7** with enol ether **35** (5 equiv) and titanium tetrachloride (4 equiv) for 4 h at −78 °C.[36] Once the reaction was completed as determined by the consumption of aldehyde **7** (TLC), a large excess of pyridine was added and the resulting reaction mixture stirred at −20 °C for 11 h (Table 1, entry 5). This procedure afforded α,β-unsaturated ketone **39** in 70% yield along with bis-TMS protected aldol addition product **37** (13%). Thus, by careful selection of the reaction temperature, the Lewis acid and the Lewis base it became possible to perform a multiple steps one-pot condensation of aldehyde-peroxide **7** with bis-TMS-enol ether **35** to form the trimethylsilyloxy-enone peroxide **39**. Slight deviation from the described reaction conditions may result in significant decrease in yield. The TMS group in **39** can be efficiently removed by HF in aqueous acetonitrile[37] to give hydroxy enone **9** (95%). Also, silylation of hydroxy enone **9** with trimethylsilyl triflate in the presence of 2,6-lutidine easily affords the TMS-protected hydroxy enone **39** (97%).

Reduction of enone **9** with $LiBH_4$ in ether was reported to give a mixture of yingzhaosu A (**1**) and its C(14) epimer

(30) (1*R*,4*R*,5*R*,8*R*)-8-Acetoxy-4,8-dimethyl-4-formyl-2,3-dioxabicyclo-[3.3.1]nonane, structurally related to aldehyde **7**, underwent slow olefination with stabilized phosphorus ylide Ph_3P=CHCOPh (6 equiv) to give after 30 days at rt the corresponding (1*R*,4*R*,5*R*,8*R*)-8-acetoxy-4,8-dimethyl-4-(3-oxo-3-phenyl-1-propenyl)-2,3-dioxabicyclo-[3.3.1]nonane (48%) and 5% recovered aldehyde. The experimental details are described in the Supporting Information. For few additional examples of Wittig reactions of structurally related bridged bicyclic endoperoxide aldehydes with semistabilized phosphorus ylides, see refs 8a,b and 11.

(31) It has been noted that olefination of less sterically hindered secondary aldehydes, having acyclic peroxide moiety, through the Horner-Emmons reaction with phosphineoxide carbanions is considerably more efficient than using Wittig's phosphorus ylides. See: Dussault, P. *Synlett* **1995**, 997−1003.

(32) For reviews on Mukaiyama aldol addition, see: (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203−301. (b) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1−200. (c) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120. (d) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65−75.

(33) Titanium tetrachloride mediated bis-aldol addition of artemether (a 1,2,4-trioxane containing a fused cyclic acetal fragment) to bis-trimethylsilyl enol-ethers has been recently applied for synthesis of highly active antimalarial and antitumor 1,2,4-trioxane dimers. See: Posner, G. H.; Ploypradith, P.; Parker, M. H.; O'Dowd, H.; Woo, S.-H.; Nortrop, J.; Krasavin, M.; Dolan, P.; Kensler, T. W.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **1999**, *42*, 4275−4280.

(34) (a) Sakai, T.; Ito, H.; Yamawaki, T.; Takeda, A. *Tetrahedron Lett.* **1984**, *25*, 2987−2988. (b) Limat, D.; Schlosser, M. *Tetrahedron* **1995**, *51*, 5799−5806.

(35) (a) According to a literature search using the SciFinder database, the only report on a one-pot Mukaiyama reaction directed toward synthesis of α,β-unsaturated ketones has been found. The reported procedure consists of the sequential treatment of an initially formed titanium aldol product with TFAA followed by triethylamine See: Bouhlel, E.; Ben Hassine, B. *Synth. Commun.* **1992**, *22*, 2183-2186. (b) $ZnCl_2$-catalyzed condensation of some silyl enol-ethers with dialkylacetals was reported to produce α, β-unsaturated ketones. See: Makin, S. M.; Kruglikova, R. I.; Tagirov, T. K.; Kharitonova, O. V. *Russ. J. Org. Chem. (Engl. Ed.)* **1984**, *20*, 1075−1078.

(36) Attempts to employ in the aldol addition the TBS-analogue of TMS-enol ether **35** were unsuccessful.

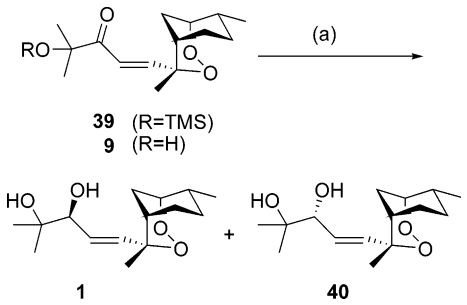
(37) (a) Boschelli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, *26*, 5239−2542. (b) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031−1069.

TABLE 2. Reduction of α,β-Unsaturated Ketones 9 and 39 under Various Conditions (Scheme 8)

entry	reduction of ketone	reaction conditions	yield (%)	ratio[a] **1**:**40**
1	**9**	1.5 equiv of $NaBH_4$, 1 equiv of $EuCl_3$, EtOH, 0 °C, 1 h	95	45:55
2	**9**	4.5 equiv of DIBAL-H, THF, −60 °C, 4 h	99[b]	45:55
3	**39**	2 equiv of *R*-BINAL-H (**41**), THF, −55 °C, 6 h	50[c,f]	55:45
4	**39**	1.1 equiv of *S*-CBS catalyst (**42a**), 1.2 equiv of catecholborane, dichloromethane/toluene, −20 °C, 16 h	97[d,f]	66:33
5	**39**	1 equiv of *S*-CBS catalyst (**42a**), 1.1 equiv of BH_3·THF, dichloromethane/toluene/THF 3:1:0.1, −40 °C, 17 h	90[e,f]	16:84
6	**39**	1.2 equiv of *S*-CBS catalyst (**42a**), 1.2 equiv of BH_3·THF, THF, −55 °C, 45 h	70[f]	11:89
7	**39**	1.2 equiv of *R*-CBS catalyst (**42b**), 1.2 equiv of BH_3·THF, THF, −55 °C, 47 h	71[f]	89:11

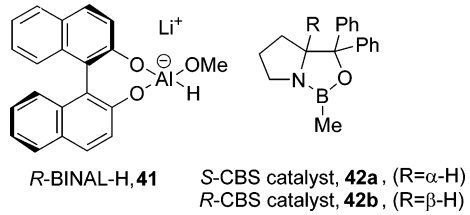
[a] The ratio was determined by ^1H NMR (400 MHz). [b] Calculated at 56% conversion. [c] Calculated at 75% conversion. [d] Calculated at 51% conversion. [e] Calculated at 70% conversion. [f] After desilylation with 2% HF in aqueous methanol or 10% HF in aqueous THF.

SCHEME 8[a]



[a] Key: (a) see details in Table 2.

40 in a 40:60 ratio (Scheme 8).[2a] In an early stage of this research,[15] we examined the suitability of other achiral reducing agents. It was found that chemoselective 1,2-reduction using the Luche procedure[38] affords yingzhaosu A (**1**) and its C(14)-epimer **40** in excellent yield, but this process is devoid of any significant stereoselectivity (Scheme 8, Table 2, entry 1). Similar results were obtained using DIBAL-H[39] in THF (Table 2, entry 2). In view of these results, we investigated the use of chiral nonracemic reducing agents. Reduction of TMS-protected enone **39** with the *R*-enantiomer of Noyroi's BINAL-H reagent (**41**)[40] followed by acidic workup did not lead to better results (Table 2, entry 3). More promising results were obtained in the reduction of **39** by boranes and the Corey/Bakshi/Shibata (CBS) catalyst (**42**).[41] Considerations relating to stereoselection and stability of the peroxide function determined that the reduction should be carried out at of low temperatures. When **39** was reduced using an equimolar amount of *S*-CBS catalyst (**42a**) and catecholborane at −20 °C in dichloromethane followed by TMS deprotection in the same vessel, yingzhaosu A (**1**) and its epimer **40** were obtained in a 2:1 ratio and high yield (Table 2, entry 4). Changing the hydride donor to the more reactive borane−THF and lowering the temperature to −40 °C resulted in a reversal and increase in stereoselection, affording yingzhaosu A (**1**) and its epimer **40** in a 16:84 ratio (Table 2, entry 5).[42] Replacing dichloromethane/toluene with THF and lowering the temperature to −55 °C further increased the diastereoselectivity (Table 2, entry 6). Below −65 °C reduction was arrested (<10% conversion after 48 h.). Finally, reduction of **39** with the enantiomeric *R*-CBS catalyst (**42b**) followed by acidic workup, afforded yingzhaosu A (**1**) as the main product in an 89:11 ratio with its epimer **40** (Table 2, entry 7).[43]



The first samples of yingzhaosu A (**1**) and its C(14) epimer **40** were obtained in our laboratory from batches deriving from the reduction of enone **9** as described in Table 2, entries 1 and 2, namely containing approximately equimolar amounts of the two diasteromers.[15] Since direct chromatographic separation between these epimers is problematic, we used a reported bypass involving the intermediacy of their corresponding carbonates **43** and **44** (Scheme 9).[2] Treatment of dihydroxy compounds **1** and **40** with carbonyldiimidazole,[44] rather than phosgene,[2] conveniently affords carbonates **43** and **44** (90% combined yield) which, after chromatographic separation, are individually deprotected by treatment with $LiBH_4$[2,45] to give yingzhaosu A (**1**, 92% yield) and its C(14)-epimer (**40**, 94% yield).

The pure samples of **1** and **40**, obtained as shown in Scheme 9, allowed us to study and develop a crystallization protocol that provides long cylindrical colorless crystals of yingzhaosu A (**1**) [mp 94−94.5 °C; $[\alpha]^{20}_D$ =

(38) (a) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459. (b) Gemal, A. L.; Luche, J. L. *Tetrahedron Lett.* **1981**, *22*, 4077−4080.

(39) Wilson, K. E.; Sediner, R. T.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1970**, 213−214.

(40) (a) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709−6716. (b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717−6725.

(41) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553.

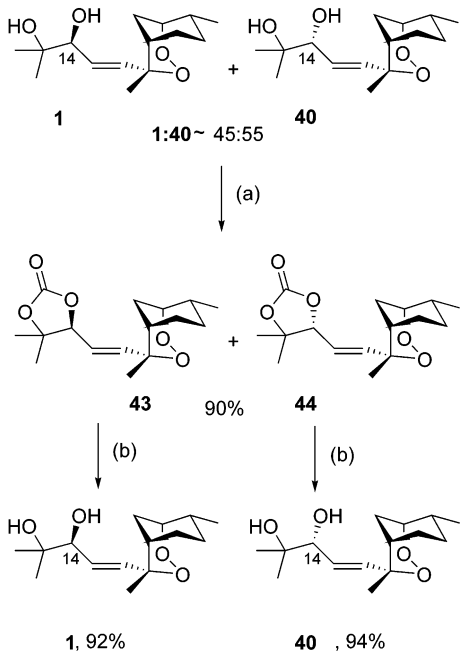
(42) Similar reversals of stereoselectivity have been reported previously. See: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987−2012 and references therein.

(43) As described herein, the use of borane−THF as the hydride donor at temperatures below −20 °C requires equimolar rather than catalytic amounts of CBS-catalyst (**42**).[42] This disadvantage was minimized by recovering from the reaction mixture the expensive amino alcohol (80%), which was used for generating the CBS reagent (**42**).

(44) (a) Kutney, J. P.; Ratcliffe, A. H. *Synth. Commun.* **1975**, *5*, 47−52. (b) Armstrong, A. In *Encyclopedia of Reagents for Organic Synthesis. Vol. 2*; Paquette, L. A. Ed.; Wiley: Chichester, 1995; pp 1006−1010.

(45) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *J. Org. Chem.* **1982**, *47*, 4702−4708.

SCHEME 9[a]



[a] Key: (a) 5 equiv of 1,1-carbonyldimidazole THF, 55 °C; (b) 2 equiv of $LiBH_4$, ether, 0 °C.

+227.4 (*c* 1.30, $CHCl_3$) [lit.[1,2] mp 95−96 °C; $[\alpha]^{25}_D = +226$ ($CHCl_3$)]] and small colorless crystals of **40**: mp 88−89 °C; $[\alpha]^{20}_D = +238.0$ (*c* 0.896, $CHCl_3$) [lit.[2] mp 55−56 °C; $[\alpha]^{20}_D = +234$ ($CHCl_3$)]. Single-crystal X-ray analysis of yingzhaosu A (**1**) confirmed the structure and relative stereochemistry (see the Supporting Information).[46] The absolute stereochemistry of the chiral centers was determined as 1*S*,4*S*,8*R*,14*S* by correlation to that of C(5), namely 5*S* as in the starting material, (*S*)-limonene (**12**). This is consistent with the previously assigned stereochemistry of yingzhaosu A (**1**).[1,2]

Since the stereoselective reductions described above provided us with products containing either mainly yingzhaosu A (**1**) or mainly **40**, it became possible to efficiently separate **1** and **40** by direct fractional recrystallization. Indeed, by this process pure yingzhaosu A (**1**) is obtained by recrystallization from *tert*-butyl methyl ether/pentane, while its C(14)-epimer **40** is obtained by recrystallization from ethyl acetate/hexane. Avoiding the intermediacy of carbonates **43** and **44** saves two synthetic steps.

These practical and effective total syntheses of yingzhaosu A (**1**) and of its C(14)-epimer **40** require just eight synthetic operations starting from (*S*)-limonene (**12**) and provide the target compounds on a preparative scale (7.3% overall yield in each case).

Biological Evaluation

Yingzhaosu A (**1**) and its C(14)-epimer **40** were assayed for *in vitro* antimalarial activity against two strains of *Plasmodium falciparum*. It was found that yingzhaosu A (**1**) showed moderate activity (IC_{50} =115 nM) against the chloroquine-resistant K1 strain, while its C(14)-epimer **40** was found to exhibit higher activity (IC_{50} = 56 nM). The activities of both compounds against the chloroquine-sensitive NF54(3D7) strain were found to be considerably lower (IC_{50} of 380 nM and 210 nM, respectively) than that of the positive drug control artemisinin (**2**, IC_{50} =2.5 nM).[47]

In vivo antimalarial assays indicated ED_{50} = 50 mg/kg for yingzhaosu A (**1**) and ED_{50} = 95 mg/kg for its C(14)-epimer **40** against chloroquine-resistant *P. yoelii* ssp. NS, as compared to ED_{50} = 5 mg/kg of sodium artesunate that was taken as positive drug control. The parallel values against chloroquine-sensitive *P. berghei* NY are ED_{50} = 250 mg/kg for yingzhaosu A (**1**), ED_{50} = 90 mg/kg for its C(14)-epimer **40**, and 4.2 mg/kg for sodium artesunate control.[48]

Preliminary *in vitro* toxicity tests against the KB nasalpharyngeal cancer cell lines showed that while cytotoxicity of yingzhaosu A (**1**) is low (ED_{50} = 36.6 μg/mL), its C(14)-epimer **40** exhibit high cytotoxicity (0.57 μg/mL). Cytotoxicity of podophyllotoxin control against this cell line is 0.00125 μg/mL.[47]

Conclusion

Twenty-five years after the discovery of yingzhaosu A (**1**), we now provide preparative-scale syntheses of this intriguing natural product, as well as of its C(14)-epimer **40**. Since the chemistry developed was adapted to the particular properties of peroxides, it can be readily applied to the synthesis of other analogues of yingzhaosu A (**1**) as well as to a variety of additional cyclic peroxides. The preliminary antimalarial and cytotoxic testing provided data, which are relevant to the structure activity relationship studies directed toward the development of new drugs.

Experimental Section

(1*S*,4*S*,5*S*)-4,8-Dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]non-7-ene (16a), (1*S*,4*R*,5*S*)-4,8-Dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]-non-7-ene (16b), (1*S*,4*S*,5*S*)-4-Methyl-8-methylidene-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]nonane (17a), and (1*S*,4*R*,5*S*)-4-Methyl-8-methylidene-4-phenylsulfenylmethyl-2,3-dioxabicyclo [3.3.1]nonane (17b). To a solution of $SOCl_2$ (4.5 equiv; 1.90 g; 16.0 mmol) and pyridine (11 equiv; 3.165 g; 40.0 mmol) in dry dichloromethane (150 mL) at 0 °C was added a solution of hydroxysulfides **8** and **15**[10a] (1.10 g; 3.74 mmol, **8**:**15** ca. 55:45) in dichloromethane (30 mL) over 1.5 h. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. At that time, the mixture was poured into cold 0.1 M HCl (100 mL) and extracted with 10% ethyl acetate/hexane (2 × 300 mL). The organic extract was washed with saturated $NaHCO_3$ (2 × 80 mL), dried (Na_2SO_4 + $NaHCO_3$), and evaporated. The residue was purified by flash chromatography (5% ethyl acetate/hexane) to give a mixture of unsaturated sulfides **16a**,**b** and

(46) Crystallographic data for the structure of yingzhaosu A (**1**) have been deposited with the Cambridge Crystallographic Data Center (CCDC) and allocated the deposition number CCDC 253141. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ca.uk).

(47) *In vitro* antimalarial and cytotoxic activities were determined by Prof. Simon L. Croft, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, U.K.

(48) *In vivo* antimalarial activity was tested on rodents. and ED_{50} values were obtained by graphic interpolations. The testing was performed by Mr. Brian L. Robinson, CTAC, Northwick Park Institute for Medical Research, Harrow, Middlesex, U.K.

17a,**b** (955 mg; total yield 92%; **16a**:**16b**:**17a**:**17b** ca. 47:39:8:6 according to the integration of the H(1) peaks in ^{1}H NMR spectrum at 400 MHz): colorless oil; R_f = 0.29 (5% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 0.7 Hz, **16a**), 1.29 (d, J = 0.6 Hz, **17a**), 1.57 (d, J = 0.5 Hz, **17b**), 1.58 (d, J = 0.8 Hz, Me(11), **16b**), total 3H; 1.55 (ddd, J = 13.1, 3.0, 2.0 Hz, **16a**), 1.63 (dddd, J = 13.0, 2.9, 2.4, 0.5 Hz, **16b**), total ca.1H; 1.79−1.81 (m, ca. 3H, **16a,b**); 1.93 (m, **16b**), 2.04 (m, **16a**), total ca. 1H; 2.15−2.37 (m), 2.48 (dddd, J = 13.0, 3.6, 3.6, 1.6 Hz, **16b**), total 3H; 2.90 (d, J = 11.8 Hz, **16b**), 3.03 (dd, J = 11.8, 0.8 Hz, **16b**), 3.00 (d, J = 12.0 Hz, **17b**) 3.10 (dd, J = 12.0, 0.5 Hz, **17b**), 3.30 (d, J = 12.2 Hz, **17a**), 3.33 (d, J = 12.7 Hz, **16a**), 3.79 (dd, J = 12.7, 0.7 Hz, **16a**), total 2H; 4.10 (br dd, J = 3.6, 2.0 Hz, ca. 0.47H, H(1)*eq*, **16a**), 4.13 (br dd, J = 3.6, 2.4 Hz, ca. 0.39H, H(1)*eq*, **16b**), 4.34 (br dd, J = 4.0, 1.4 Hz, ca. 0.08H, H(1)*eq*, **17a**), 4.40 (br dd, J = 4.3, 1.7 Hz, ca. 0.06H, H(1)*eq*, **17b**), total 1H; 4.89 (m, ca. 0.3 H, **17a,b**), 5.73 (m, **16b**), 5.75 (m, **16a**), total ca. 1H; 7.18−7.46 (m, 5H). The major component **16a** was purified by additional semipreparative reversed-phase HPLC (60% MeCN/H_2O).

(1*S*,4*S*,5*S*)-4,8-Dimethyl-4-phenylsulfenylmethyl-2,3-dioxabicyclo[3.3.1]non-7-ene (16a): white waxy solid; mp 61−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 0.7 Hz, 3H, Me(11)), 1.55 (ddd, J = 13.1, 3.0, 2.0 Hz, 1H, H(9)*ax*), 1.80 (ddd, J = 2.7, 1.6, 1.6 Hz,, 3H, Me(10)), 2.04 (m, 1H, H(5)*eq*), 2.21 (dddq, J = 19.0, 5.4, 2.7, 2.7 Hz, 1H, H(6)*ax*), 2.30 (dddd, J = 13.1, 3.6, 3.6, 1.6 Hz, 1H, H(9)*eq*), 2.33 (dddq, J = 19.0, 6.4, 1.6, 1.6 Hz, 1H, H(6)*eq*), 3.34 (d, J = 12.7 Hz, 1H, H(12)), 3.79 (d, J = 12.7, 0.7 Hz, 1H, H′(12)), 4.10 (br dd, J = 3.6, 2.0 Hz, 1H, H(1)*eq*), 5.76 (m, 1H, H(7)), 7.19 (m, 1H, Ar), 7.29 (m, 2H, Ar), 7.42 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (Me(10)), 22.7 (Me(11)), 26.4 (C(9)H_2), 27.6 (C(6)H_2), 28.5 (C(5)H), 40.7 (C(12)H_2), 76.2 (C(1)H), 83.4 (C(4)), 126.2 (CH, Ar), 126.8 (C(7)H), 128.9 (2 × CH, Ar), 129.7 (2 × CH, Ar), 131.3 (C(8)), 137.0 (C, Ar); HRMS calcd for $C_{16}H_{21}O_2S$ (MH^+) 277.1262, found 277.1253,.

(1*S*,4*S*,5*S*)-4,8-Dimethyl-4-phenylsulfinylmethyl-2,3-dioxabicyclo[3.3.1]non-7-enes (18a,b), (1*S*,4*R*,5*S*)-4,8-Dimethyl-4-phenylsulfinylmethyl-2,3-dioxabicyclo[3.3.1]-non-7-enes (18c,d), (1*S*,4*S*,5*S*)-4-Methyl-8-methylene-4-phenylsulfinylmethyl-2,3-dioxabicyclo[3.3.1]nonanes (19a,b), and (1*S*,4*R*,5*S*)-4-Methyl-8-methylene-4-phenylsulfinylmethyl-2,3-dioxabicyclo[3.3.1]nonanes (19c,d). To a solution of sulfides **16a**,**b** and **17a**,**b** (2.95 g; 10.67 mmol) in ethyl acetate (200 mL) at −50 °C was added a solution of *m*-CPBA (ca. 1.06 equiv; 3.25 g of ca. 60% purity, ca. 11.3 mmol) in ethyl acetate (120 mL) over 20 min. The mixture was stirred at −50 to −30 °C for 1.5 h and then poured into 5% Na_2CO_3 (60 mL), extracted with ethyl acetate (4 × 50 mL), dried (Na_2SO_4), and evaporated. Flash chromatography (40% ethyl acetate/hexane) afforded a mixture of eight sulfoxides **18a**−**d** and **19a**−**d** (2.94 g; 94% yield) as a yellowish viscous oil, which was used directly in the next step without separation of the isomers. A sample of the mixture of the eight sulfoxides was separated by MPLC (gradient: 20%−50% ethyl acetate/hexane) for analytical purposes to give three fractions. (i) The least polar fraction was a colorless solid containing **18c** and **19c** (**18c**:**19c** ca. 85: 15): mp. 136−139 °C; R_f = 0.49 (50% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (ddd, J = 13.4, 3.1, 1.9 Hz), 1.70 (ddd, J = 13.1, 3.0, 2.2 Hz), total 1H; 1.79 (br dd, J = 3.8, 2.0, ca. 2.55 H); 1.81 (br d, J = 0.55 Hz, ca. 0.45H), 1.82 (br d, J = 0.65 Hz, 2.55H), total 3H; 2.08 (m, ca. 0.15H); 2.16 (m), 2.19 (m), total 1H; 2.27−2.42 (m, total ca. 2.3H); 2.60 (dddd, J = 13.2, 3.5, 3.5, 1.2 Hz, ca. 0.85H); 2.67 (m, ca. 0.15H); 2.77 (dd, J = 13.5, 0.65 Hz), 2.86 (dd, J = 13.4, 0.55 Hz), total 1H; 2.88 (d, J = 13.5 Hz), 2.97 (d, J = 13.4 Hz), total 1H; 4.17 (br dd, J = 3.5, 1.9 Hz, 0.85H), 4.44 (br dd, J = 3.5, 1.5 Hz, 0.15H), total 1H; 4.93 (br s, ca. 0.15H), 4.94 (br s, ca. 0.15H), total ca. 0.3H; 5.73 (m, ca. 0.85H); 7.47−7.56 (m, 3H), 7.62−7.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (CH_3), 23.2 (CH_3), 26.3 (CH_2), 27.2 (CH_2), 27.9 (CH_2), 29.8 (CH_2), 30.3 (CH_2), 30.4 (CH), 31.6 (CH), 65.5 (CH_2), 65.5 (CH_2), 76.8 (CH), 80.8 (CH), 82.2 (C), 113.3 (CH_2), 123.7 (CH), 123.8 (CH), 126.0 (CH), 129.4 (CH), 129.5 (CH), 131.3 (CH), 131.4 (CH), 131.8 (C), 144.7 (C), 146.1 (C). (ii) The second fraction consists of a colorless oil: R_f = 0.43 (50% ethyl acetate/hexane) containing four isomers, **18a**, **19a**, **18d**, and **19d** (**18**:**19** ca.94:6; **18a**:**18d** ca.55:45): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (br d, J = 0.7 Hz), 1.88 (br s), 1.90 (br s), total 3H; 1.56 (m), 1.63 (ddd, J = 13.1, 3.2, 2.1 Hz), 1.75 (ddd, J = 13.4, 2.4, 2.4 Hz), total ca.1H; 1.77 (m), 1.79 (m), total ca. 3H; 1.99 (m, ca. 0.5H), 2.20 (m, ca.0.5H); 2.26−2.34 (m, total ca.0.85H); 2.36−2.48 (m, *ca.* 2H); 2.53−2.59 (m, total ca.0.5H), 2.55 (d, J = 13.8 Hz, ca. 0.4H), 3.13 (d, J = 13.9 Hz, ca. 0.5H), total ca. 1H; 3.08 (br d, J = 13.8 Hz, ca. 0.4H), 3.13 (br d, J = 13.8 Hz), 3.66 (dd, J = 13.9, 0.7 Hz, ca.0.5H), total 1H; 4.15 (m, 0.94H), 4.43 (m, 0.06H), total 1H; 4.90 (br s, ca.0.12H), 5.68 (m, ca.0.4H), 5.78 (m, ca.0.5H), 7.46−7.56 (m, 3H), 7.61−7.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 21.9 (CH_3), 22.1 (CH_3), 24.1 (CH_3), 26.2 (CH_2), 26.5 (CH_2), 27.4 (CH_2), 27.8 (CH_2), 29.2 (CH), 31.5 (CH), 64.8 (CH_2), 66.2 (CH_2), 76.4 (CH), 77.1 (CH), 80.9 (CH), 81.9 (C), 82.1 (C), 113.1 (CH_2), 123.7 (CH), 123.8 (CH), 126.6 (CH), 126.9 (CH), 129.3 (CH), 129.3 (CH), 131.99 (C), 131.01 (CH), 131.06 (CH), 131.09 (C), 144.6 (C), 144.8 (C), 146.3 (C). The most polar fraction consists of a colorless oil, R_f = 0.35 (50% ethyl acetate/hexane) containing the two isomers **18b** and **19b** (**18b**:**19b** ca.91:9). Isomers **18b** and **19b** were separated by additional MPLC (40% ethyl acetate/hexane) to afford isomer **19b** (ca.95% purity) as a colorless waxy solid and isomer **18b** as a colorless solid. Isomer **19b**: white waxy solid; mp 78−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (m, 1H, H(9)*ax*), 1.61 (br s, 3H, Me(11)), 1.72 (dddd, J = 13.8, 13.8, 6.4, 3.7 Hz, 1H, H(6)*ax*), 2.04 (dddd, J = 6.4, 6.4, 3.2, 3.2 Hz, 1H, H(5)*eq*), 2.18 (m, J = 13.8 Hz, 1H, H(6)*eq*), 2.41 (br dd, J = 15.2, 6.0 Hz, 1H, H(7)*eq*), 2.51 (br ddd, J = 13.6, 6.4, 3.5 Hz, 1H, H(9)*eq*), 3.06 (m, 1H, H(7)*ax*), 3.28 (br d, J = 14.0 Hz, 1H, H(12)), 3.50 (br d, J = 14.0 Hz, H(12′)), 4.37 (br dd, J = 3.5, 1.5 Hz, 1H, H(1)*eq*), 4.93 (br dd, J = 2.2, 2.2 Hz, 1H, H(10)), 4.96 (m, 1H, H(10′)), 7.52 (m, 1H, Ar), 7.55 (m, 2H, Ar), 7.69 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5 (C(11)H_3), 27.0 (C(6)H_2), 30.1 (C(9)H_2), 30.5 (C(7)H_2), 31.7 (C(5)H), 66.2 (C(12)H_2), 80.6 (C(1)H), 82.5 (C(4)), 113.6 (=C(10)H_2), 123.9 (2 × CH, Ar), 129.3 (2 × CH, Ar), 130.9 (CH, Ar), 146.2 (C(13)), 154.6 (=C(8)). Isomer **18b**: white solid; mp 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (br s, 3H, Me(11)), 1.64 (ddd, J = 13.3, 3.0, 2.2 Hz, 1H, H(9)*ax*), 1.79 (ddd, J = 2.7, 1.6, 1.6 Hz, 3H, Me(10)), 1.99 (m, 1H, H(5)*eq*), 2.23 (dddq, J = 19.2, 5.4 Hz, 1.6, 1.6 Hz, 1H, H(6)*ax*), 2.37−2.47 (m, 2H, H(6)*eq* + H(9)*eq*), 3.30 (d, J = 14.0 Hz, 1H, H(12)), 3.44 (dd, J = 14.0, 0.35 Hz, 1H, H(12′)), 4.12 (m, 1H, H(1)*eq*), 5.78 (m, 1H, H(7)), 7.50 (m, 1H, Ar), 7.53 (m, 2H, Ar), 7.68 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (C(10)H_3), 22.7 (C(11)H_3) 26.5 (C(9)H_2), 27.4 (C(6)H_2), 31.0 (C(5)H), 66.1 (C(12)H_2), 76.5 (C(1)H), 81.8 (C(4)), 123.8 (2 × CH, Ar), 127.0 (=C(7)H), 129.3 (2 × CH, Ar), 130.8 (CH, Ar), 131.6 (=C(8)), 144.9 (C, Ar).

(1*S*,4*S*,5*S*)-4,8-Dimethyl-2,3-dioxabicyclo[3.3.1]non-7-ene-4-carbaldehyde (21), (1*S*,4*S*,5*S*)-4-Methyl-8-methylene-2,3-dioxabicyclo[3.3.1]nonane-4-carbaldehyde (22), (1*S*,4*R*,5*S*)-4,8-Dimethyl-2,3-dioxabicyclo[3.3.1]non-7-ene-4-carbaldehyde (23), and (1*S*,4*R*,5*S*)-4-Methyl-8-methylene-2,3-dioxabicyclo[3.3.1]nonane-4-carbaldehyde (24). A solution of **18a**−**d** and **19a**−**d** (1.25 g; 4.3 mmol) and 2,6-lutidine (10 equiv; 5 mL; 43 mmol) in dry dichloromethane (135 mL) under argon was cooled to −40 °C, and trifluoroacetic anhydride (5 equiv; 3 mL; 21.4 mmol) was added over 15 min. The yellow reaction mixture was stirred for 1 h at −40 to −30 °C and 420 mL of cold pentane added. The solution was washed with 50 mL of saturated $NaHCO_3$, and the solvent was removed on a rotary evaporator at 0.3−0.5 bar and 40 °C to give a yellow oil. The oil was dissolved in methanol/dichloromethane (1:10 mixture; 135 mL) and cooled to −10 °C. Morpholine (1 equiv; 0.4 mL; 4.2 mmol) was added and the

reaction mixture stirred at −10 to 0 °C for 2 h. Pentane (350 mL) was added, and the solution was washed with 0.1 M HCl (100 mL) and saturated $NaHCO_3$ (50 mL). Upon drying (Na_2SO_4), the solvent was removed on a rotary evaporator at 0.3 bar and 40 °C to give an oil consisting of a mixture of unsaturated aldehydes **21**−**24**. The mixture was fractionated by three flash chromatograhies (gradient: 0% to 6% ethyl acetate/hexane) to afford one fraction containing unsaturated aldehydes **21** and **22** as a colorless oil (335 mg; 43% yield; **21**:**22** ca. 83:17 as determined from the integration of the H(1) and Me(11) peaks) and a fraction containing a mixture of unsaturated aldehydes **23** and **24** as a white solid (239 mg; 31% yield; **23**:**24** ca. 83:17 as estimated from the integration of the Me(11) signals).

Characterization. Mixture of aldehydes **21** and **22** (**21**:**22** ca.83:17): colorless oil; R_f = 0.30 (6% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, **21**, Me(11)), 1.17 (s, **22**, Me(11)), total 3H; 1.59 (ddd, J = 13.4, 3.0, 2.1, **22**, H(9)*ax*), 1.65 (ddd, J = 13.1, 3.0, 2.1 Hz, **21**, H(9)*ax*), total 1H; 1.71−1.82 (m, ca. 0.4H, **22**, H(6)*eq* +H(5)*eq*); 1.83 (dd, J = 4.2, 2.2, ca. 2.5H, **21**, Me(10)); 2.05 (dddd, J = 13.1, 3.5, 3.5, 1.2 Hz, **21**, H(9)*eq*), 2.15 (ddd, J = 13.4, 6.7, 3.3 Hz, **22**, H(9)*eq*), total 1H; 2.23 (m, ca. 0.8H, **21**, H(5)*eq*), 2.25 (m, ca. 0.8H, **21**, H(6)-*eq*), 2.30 (dddq, J = 19.0, 5.3, 2.6, 2.2 Hz, ca. 0.8H, **21**, H(6)-*ax*), 2.41 (br dd, J = 14.9, 6.7 Hz, ca.0.2H, **22**, H(7)*eq*), 3.01 (ddddd, J = 14.9, 14.9, 7.4, 2.5, 2.5 Hz, *ca.* 0.2H, **22**, H(7)*ax*), 4.14 (m, 0.83H, **21**, H(1)*eq*), 4.38 (m, 0.17H, **22**, H(1)*eq*), 4.96 (dd, J = 2.5, 2.5 Hz, ca.0.2H, **22**, H(10)), 4.99 (m, J = 2.5, 2.5, 0.5 Hz, ca. 0.2H, **22**, H(10′), 5.81, (m, ca. 0.8H, **21**, H(7), 9.91 (s, 1H, **21** + **22**, H(12), aldehyde); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1 (**22**, C(11)H_3), 18,2 (**21**, C(11)H_3), 21.3 (**21**, C(10)H_3), 25.9 (**22**, C(9)H_2), 26.3 (**21**, C(9)H_2), 27.3 (**21**, C(5)H), 28.0 (**21**, C(6)H_2), 28.1 (**22**, C(5)H), 30.3 (**22**, C(6)H_2), 31.6 (**22**, C(7)H_2), 76.7 (**21**, C(1)H), 80.7 (**22**, C(1)H), 88.4 (**21**, C(4)), 89.0 (**22**, C(4)), 114.2 (**22**,=C(10)H_2), 127.3 (**21**, =C(7)H), 130.9 (**21**, =C(8)), 145.6 (**22**, =C(8)), 205.5 (**21**, C(12)H=O), 205.6 (**22**, C(12)H, aldehyde); IR (neat) ν 2931 (m), 2874 (m), 2850 (m), 2836 (m), 2803 (m), 1736 (s), 1450 (m), 1440 (m), 1370 (m), 1108 (m) 1009 (m) cm^{-1}; MS (*m/z*) 183.10 (MH^+, 2), 155.16 (21), 139.09 (100), 127.14 (43); HRMS calced for $C_{10}H_{15}O_3$ [MH^+] 183.1021, found 183.1017.

Mixture of aldehydes **23** and **24** (**23**:**24** ca.83:17): white solid; mp 49−50 °C; R_f = 0.14 (6% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 0.51H, **24**, Me(11)) 1.56 (s, 2.49H, **23**, Me(11)), total 3H; 1.65 (m, **24**, H(9)*ax*), 1.67 (br ddd, J = 13.1, 2.9, 2.1 Hz, **23**, H(9)*ax*) total 1H; 1.71−1.83 (m, ca. 0.2H, **24**, H(6)), 1.84 (dd, J = 4.2, 2.2, ca. 2.8 H, **23**, Me(10); 1.87−1.95 (m, ca.0.4H, **24**, H(6) + H(5)*eq*), 2.08 (m, J = 1.6, 1.4 Hz, ca.0.8H, **23**, H(6)*eq*), 2.10 (m, ca.0.8H, **23**, H(5)*eq*), 2.26 (dddq, J = 19.3, 8.3, 2.9, 2.9 Hz, ca.0.8H, **23**, H(6)*ax*); 2.32 (m, *ca.* 0.2H, **24**, H(9)*eq*), 2.47 (dddd, J = 13.1, 3.6, 3.6, 1.6 Hz, ca.0.8H, **23**, H(9)*eq*), total 1H; 2.53 (ddddd, J = 13.3, 4.0, 3.4, 3.4, 0.6 Hz, ca.0.2H, **24**, H(7)*eq*), 2.73 (br m, ca.0.2H, **24**, H(7)-*ax*), 4.19 (m, 0.83H, **23**, H(1)*eq*), 4.61 (m, J = 4.5, 0.5 Hz, 0.17H, **24**, H(1)*eq*), total 1H; 4.92 (m, ca.0.4H, **24**, 2 × H(10), 5.74 (m, ca.0.8H, **23**, H(7), 9.46 (s, 1H, **23** + **24**, H(12), aldehyde); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (**23**, C(10)H_3), 21.3 (**23**, C(11)-H_3), 25.7 (**23**, C(9)H_2), 28.5 (**23**, C(6)H_2), 29.8 (**23**, C(5)H), 77.0 (**23**, C(1)H), 88.1 (**23**, C(4)), 112.7 (**24**, =C(10)H_2), 126.8 (**23**, =C(7)H), 130.0 (**23**, =C(8)), 202.1 (**23**, C(12)H, aldehyde); IR (neat) ν 2962 (w), 2922 (m), 2833 (w), 2815 (w), 1734 (s), 1446 (s), 1377 (m), 1363 (w), 1101 (m) 1088 (m) cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.63; H, 7.98.

(1*S*,4*S*,5*S*)-4-Dimethoxymethyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]non-7-ene (25) and (1*S*,4*S*,5*S*)-4-Dimethoxymethyl-4-methyl-8-methylene-2,3-dioxabicyclo[3.3.1]nonane (26). A mixture of unsaturated aldehydes **21** and **22** (78 mg; 0.428 mmol, **21**:**22** ca. 92:8) was dissolved in trimethylorthoformate (2.0 mL), Amberlyst-15 (200 mg) was added, and the resulting mixture was stirred for 24 h at room temperature. The reaction mixture was filtered through Celite and the Celite washed with 30 mL of dichloromethane. The filtrate was dried (Na_2SO_4 + $NaHCO_3$), the drying material filtered off, and the solvent removed under reduced pressure. Flash chromatography (17% ethyl acetate/hexane) afforded an inseparable mixture of unsaturated acetals **25** and **26** (92 mg; 94%; **25**:**26** ca. 91:9) as a white solid: mp 67−69 °C; R_f = 0.32 (17% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, ca.2.75H, **25**, Me(11)), 1.14 (s, ca. 0.25H, **26**, Me(11)), total 3H; 1.55 (ddd, J = 12.5, 3.0, 2.0 Hz, **26**, H(9)*ax*), 1.62 (ddd, J = 13.1, 3.0, 2.1 Hz, **25**, H(9)*ax*), total 1H; 1.80 (ddd, J = 2.6, 1.5, 1.5 Hz, ca. 2.7H, **25**, Me(10)), 2.01 (m, 1H, **25** + **26**, H(5)-*eq*), 2.18 (dddq, J =19.0, 5.5, 2.6, 2.6 Hz, ca. 0.9H, **25**, H(6)-*eq*), 2.31 (dddq J = 19.0, 4.8, 1.6, 1.6, ca. 0.9H, **25**, H(6)*ax*) 2.32−2.38 (m, ca. 0.9H, **25**, H(9)*eq*), 2.39−2.44 (m, 0.1H, **26**, H(7)), 3.05 (m, 0.1H, **26**, H(7)); 3.47 (s, 0.3H, **26**, OCH_3), 3.48 (s, 2.7H, **25**, OCH_3), 3.66 (s, 0.3H, **26**, OCH_3), 3.69 (s, 2.7H, **25**, OCH_3) total 6H; 4.14 (m, *ca.* 0.9 H, **25**, H(1)*eq*), 4.40 (m, 0.1H, **26**, H(1)*eq*), total 1H; 4.91 (m, ca.0.1H, **26**, H(10)), 4.93 (m, ca.0.1H, **26**, H(10)), 5.00 (s, ca.0.9H, **25**, H(12)), 5.77 (m, *ca.* 0.9H, **25**, H(7)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2 (**26**, C(11)H_3), 15.5 (**25**, C(11)H_3), 21.1 (**25**, C(10)H_3), 26.6 (**25**, C(9)-H_2), 27.4 (**26**, C(9)H_2), 27.5 (**25**, C(5)H), 27.7 (**25**, C(6)H_2), 28.3 (**26**, C(5)H), 30.1 (**26**, C(6)H_2), 30.3 (**26**, C(7)H_2), 56.5 (**25** + **26**, 2 × OCH_3), 59.1 (**26**, OCH_3) 59.3 (**25**, OCH_3), 76.3 (**25**, C(1)H), 80.4 (**26**, C(1)H), 85.2 (**25**, C(4)), 85.9 (**26**, C(4)), 104.3 (**25** + **26**, =C(12)H), 112.9 (**26**, C(10)H_2) 127.1 (**25**, =C(7)H), 131.1 (**25**, =C(8)), 146.9 (**26**, =C(8)). Anal. Calcd for C_{12}-$H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.19; H, 8.95.

(1*S*,4*S*,5*S*,8*R*)-4-Dimethoxymethyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonane (27). A mixture of unsaturated acetals **25** and **26** (118 mg, 0.517 mmol; **25**:**26** ca. 10:1) was dissolved in ethyl acetate (20 mL). Platinum(IV) oxide (0.1 equiv; 12 mg) was added and the reaction mixture cooled to −20 °C. A hydrogen atmosphere was introduced by flushing the system three times, and a hydrogen pressure of 1 atm was maintained throughout the reaction. The temperature was allowed to rise, and the reaction mixture was stirred at −8 to −12 °C until hydrogen consumption ceased (1 h). The reaction mixture was then cooled to −78 °C, the hydrogen was removed in vacuo, and the system was flushed several times with air. The reaction mixture was filtered through a plug of cotton and concentrated at 0.2 bar and 40 °C. The resulting oil was purified by flash chromatography (7.5% ethyl acetate/hexane) to give acetal **27** as a colorless oil (96 mg; 81%): R_f = 0.29 (7.5% ethyl acetate/hexane); $[\alpha]^{20}_D$ = 198.0 (*c* 0.210, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 3H, Me(11)), 1.10 (d, J = 6.8 Hz, 3H, Me(10)), 1.47 (ddd, J = 13.2, 3.0, 1.6 Hz, 1H, H(9)*ax*), 1.55−1.67 (m, 2H, H(6)*eq* + H(7)), 1.76−1.87 (m, 1H, H(8)*ax*), 1.90 (ddd, J = 6.3, 3.1, 3.1 Hz, 1H, H(5)*eq*), 1.95−2.05 (m, 2H, H(6)*ax* + H(7′)), 2.32 (dddd, J = 13.1, 6.6, 4.2, 4.2 Hz, 1H, H(9)*eq*), 3.47 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.88 (m, 1H, H(1)*eq*), 4.97 (s, 1H, H(12)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8 (C(10)H_3), 18.5 (C(11)H_3), 27.2 (CH_2), 27.9 (C(8)H), 29.5 (CH_2), 29.7 (CH_2), 35.6 (C(5)H), 56.6 (OCH_3), 59.2 (OCH_3), 79.3 (C(1)H), 85.1 (C(4)), 104.4 (C(12)H, acetal); IR (neat) ν 3000 (w), 2874 (m), 2955 (s), 2950 (m), 2844 (w), 2827 (w), 1468 (w), 1455 (m), 1379 (w), 1368 (w), 1191 (m), 1187 (m), 1110 (m), 1082 (m), 1074 (s) cm^{-1}; MS (*m/z*) 231.15 (MH^+, 0.3), 199.12 (M − CH_3OH, 28) 139.10 (19), 95.08 (27), 83.94 (48), 75.04 ($CH^+(OCH_3)_2$, 100); HRMS calcd for $C_{12}H_{22}O_4$ [MH^+] 231.1749, found 231.1820.

Synthesis of (1*S*,4*S*,5*S*,8*R*)-4,8-Dimethyl-2,3-dioxabicyclo[3.3.1]nonane-4-carbaldehyde (7) by Deacetalization of 27. To a solution of acetal **27** (48 mg; 0.208 mmol) in dichloromethane (5 mL) were added toluenesulfonic acid (2.5 equiv; 100 mg; 0.53 mmol) and glyoxalic acid monohydrate (25 equiv; 0.480 g; 5.2 mmol). The resulting heterogeneous mixture was stirred for 18 h. The solution was decanted into another flask and the solid residue washed with 3 × 2 mL dichloromethane. The resulting solution was filtered through a short plug of silica gel with 40 mL of dichloromethane. The solvent was removed under reduced pressure (40 °C, 0.2 bar) to afford the desired aldehyde **7** as a white solid (35.5 mg; 93%): mp

77−78 °C; R_f = 0.46 (10% ethyl acetate/hexane); $[\alpha]^{20}_D$ = 284.1 (*c* 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 3H, Me-(11)), 1.12 (d, *J* = 6.6 Hz, 3H, Me(10)), 1.51 (ddd, *J* = 13.1, 3.0, 1.8 Hz, 1H, H(9)*ax*), 1.66−1.76 (m, 2H, H(6) + H(7)), 1.87 (m, 1H, H(8)*ax*), 1.91−2.00 (m, 2H, H(6′) + H(7′)), 2.04 (dddd, *J* = 13.1, 3.8, 3.8, 2.4 Hz, 1H, H(9)*eq*), 2.11 (dddd, *J* ≈ 3.8, 3.0, 3.0, 3.0 Hz, 1H, H(5)*eq*), 3.87 (m, 1H, H(1)*eq*), 9.89 (s, 1H, H(12)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8 (C(10)H_3), 18.5 (C(11)H_3), 25.7 (CH_2), 27.9 (C(5)H), 29.5 (CH_2), 31.2 (CH_2), 35.1 (C(8)H), 79.7 (C(1)H), 88.3 (C(4)), 206.1 (C(12)H=O); IR (KBr) ν 2962 (s), 2949 (s), 2927 (s), 2872 (m), 2808 (m), 1740 (s), 1455 (m), 1382 (m), 1362 (w), 1349 (w), 1333 (w), 1126 (m), 1103 (m), 1048 (w), 1001 (m) cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.14; H, 8.85.

Synthesis of (1*S*,4*S*,5*S*,8*R*)-4,8-Dimethyl-2,3-dioxabicyclo[3.3.1]nonane-4-carbaldehyde (7) by Direct Hydrogenation of Unsaturated Aldehydes 21 and 22. A mixture of unsaturated aldehydes **21** and **22** (40 mg, 0.22 mmol; **21**:**22** ca. 83:17) was dissolved in ethyl acetate (20 mL). Platinum-(IV) oxide (0.15 equiv; 8 mg) was added and the reaction mixture cooled to −20 °C. A hydrogen atmosphere was introduced by flushing the system three times, and a hydrogen pressure of 1 atm was maintained throughout the reaction. The temperature was allowed to rise to −8 °C and kept at this temperature for 1 min until the color of the catalyst had changed from brown to black. The reaction was then cooled to −11 °C and stirred in the temperature interval −11 to −12 °C for 50 min by which time hydrogen consumption ceased. The reaction was then cooled to −78 °C, the hydrogen atmosphere removed in vacuo, and the system flushed several times with air. The reaction mixture was filtered through a plug of cotton, and the solvent removed under reduced pressure (0.2 bar, 40 °C). The resulting oil was purified by flash chromatography (15% ether/pentane) to give aldehyde **7** as a white solid (36 mg; 90% yield). Analytical data as above.

Synthesis of (1*S*,4*R*,5*S*)-4-Dimethoxymethyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]non-7-ene (28) and (1*S*,4*R*,5*S*)-4-Dimethoxymethyl-4-methyl-8-methylene-2,3-dioxabicyclo[3.3.1]nonane (29). Acetals **28** and **29** were prepared according to the procedure for the preparation of acetals **25** and **26** described above. Thus, the acetalization of 210 mg (1.15 mmol) of a mixture of unsaturated aldehydes **23** and **24** (**23**:**24** 83:17) afforded an inseparable mixture of acetals **28** and **29** (251 mg; 96% yield; ratio 91:9) as a colorless oil: R_f = 0.29 (15% ether/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 0.3H, Me(11), **29**), 1.45 (s, 2.7H, Me(11), **28**), total 3H; 1.50 (ddd, *J* = 13.2, 3.3, 1.7 Hz, 0.1H, **29**), 1.56 (ddd, *J* = 13.0, 3.2, 2.1 Hz, 0.9H, H(9)*ax* **28**), total 1H; 1.80 (ddd, *J* = 2.6, 1.5, 1.5 Hz, ca. 2.7H, Me(10) **28**), 1.79−1.83 (m. 1H, H(5)*eq*, **28** + **29**); 2.01 (m, ca. 0.1H, **29**), 2.14 (dddq, *J* = 19.0, 5.5, 2.6, 2.6 Hz, ca. 0.9H, H(6) **28**), total 1H; 2.22 (dddq, *J* = 19.0, 4.8, 1.7, 1.7 Hz, 1H, H(6) **28** + **29**), 2.45 (dddd, *J* = 13.0, 3.6, 3.6, 1.5 Hz, 0.9H, H(9)*eq* **28**); 3.44 (s, 2.7H, OCH_3, **28**), 3.46 (s, 0.3H, **29**), 3.48 (s, 2.7H, OCH_3, **28**), 3.53 (s, 0.3H, **29**), total 6H; 4.04 (s, 0.9H, H(12), **28**), 4.23 (s, 0.1H, **29**), total 1H; 4.09 (m, ca. 0.9 H, H(1) **28**), 4.42 (br d, *J* = 3.7 Hz, 0.1H, **29**), total 1H; 4.93 (m, 0.2H, =CH_2 **29**), 5.74 (m, 0.9H, =C(7)H **28**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4 (**28**, C(11)H_3), 15.6 (**29**, C(11)H_3), 21.3 (**28**, C(10)H_3), 26.7 (**29**, C(9)H_2), 26.9 (**28**, C(9)H_2), 27.4 (**28**, C(6)-H_2), 29.5 (**28**, C(5)H), 30.2 (**29**, CH_2), 30.9 (**29**, CH_2), 31.0 (**29**, C(5)H), 56.3 (**29**, OCH_3), 56.4 (**28**, OCH_3), 58.8 (**28**, OCH_3) 59.0 (**29**, OCH_3), 76.7 (**28**, C(1)H), 80.7 (**29**, C(1)H), 86.0 (**28**, C(4)), 87.1 (**29**, C(4)), 106.5 (**29**, OC(12)HO), 106.6 (**28**, OC(12)HO), 112.5 (**29**, =C(10)H_2), 126.8 (**28**, =C(7)H), 131.3 (**28**, =C(8)), 146.8 (**29**, =C(8)); IR (neat) ν 2991 (w), 2958 (s), 2934 (s), 2914 (m), 2881 (w), 2835 (m), 1466 (w), 1451 (m), 1382 (w), 1368 (m), 1348 (w), 1324 (w), 1208 (m), 1185 (w), 1170 (w), 1160 (w), 1111 (s), 1082 (s), 1025 (w), 1013 (m), 982 (m) cm^{-1}.

(1*S*,4*R*,5*S*,8*R*)-4-Dimethoxymethyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonane (30). Acetal **30** was prepared according to the procedure for the preparation of acetal **27** described above. Thus, the hydrogenation of a mixture of unsaturated acetals **28** and **29** (135 mg; 0.591 mmol; **28**:**29** ca. 83:17) afforded acetal **30** (104 mg; 77% yield) as white solid: mp 38−40 °C; R_f = 0.29 (15% ether/hexane); $[\alpha]^{20}_D$ = 145.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 1.01 (ddd, *J* = 13.0, 3.2, 1.6 Hz, 1H, H(9)*ax*), 1.16 (d, *J* = 6.8 Hz, 3H, Me-(10)), 1.40 (dddd, *J* = 13.9, 13.9, 6.4, 3.4, 1H, H(6)*ax*), 1.46 (dqdd, *J* = 13.6, 6.8, 6.4, 3.0 Hz, 1H, H(8)*ax*), 1.57 (ddd, *J* = 13.1, 6.4, 6.4 Hz, 1H, H(7)*eq*), 1.69 (s, 3H, Me(11)), 1.71 (dddd, *J* = 3.2, 3.2, 3.2, 3.2 Hz, 1H, H(5)*eq*), 1.94 (m, 1H, H(6)*eq*), 2.13 (dddd, *J* = 13.9, 13.6, 13.3, 6.0 Hz, 1H,H(7)*ax*), 2.21 (dddd, *J* = 12.3, 4.3, 4.3, 3.3 Hz, 1H, H(9)*eq*), 3.13 (s, 3H, OMe), 3.31 (s, 3H, OMe), 3.59 (m, 1H, H(1)*eq*), 4.08 (s, 1H, H(12)); ^{13}C NMR (100 MHz, C_6D_6) δ 16.1 (C(11)H_3), 19.0 (C(10)H_3), 26.9 (C(6)H_2), 30.1 (C(9)H_2), 30.81 (C(5)H), 30.84 (C(7)H_2), 35.9 (C(8)H), 56.5 (OCH_3), 58.6 (OCH_3), 79.2 (C(1)H), 86.6 (C(4)), 106.7 (C(12)H, acetal); IR (KBr) ν 3006 (w), 2989 (w), 2950 (s), 2962 (s), 2947 (s), 2918 (m), 2870 (m), 2830 (w), 1467 (m), 1446(m), 1385 (w), 1366 (m), 1348 (w), 1326 (w), 1318 (w), 1207 (w), 1188 (w), 1172 (w), 1153 (w), 1126 (m), 1101 (m), 1085 (s), 1049 (w) cm^{-1}; MS (*m*/*z*) 230.15 (M^+, 1.3), 199.12 (M-CH_3-OH, 28) 149.02 (18), 95.08 (11), 83.95 (85), 75.04 ($CH(OCH_3)_2$, 100); HRMS calcd for $C_{12}H_{22}O_4$ [M^+] 230.1518, found 230.1530.

(1*S*,4*R*,5*S*,8*R*)-4,8-Dimethyl-2,3-dioxabicyclo[3.3.1]-nonane-4-carbaldehyde (31). Aldehyde **31** was prepared by deacetalization of acetal **30** according to the procedure for deacetalization of acetal **27** described above. Thus, deacetalization of 62 mg (0.269 mmol) of acetal **30** afforded aldehyde **31** (49 mg; 98% yield) as a colorless oil: R_f = 0.30 (6% ethyl acetate/hexane); $[\alpha]^{20}_D$ = 172.1 (*c* 0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.5 Hz, 3H, Me(10)), 1.46 (s, 3H, Me(11)), 1.52 (ddd, *J* = 13.2, 3.1, 1.5 Hz, 1H, H(9)*ax*), 1.56−1.69 (m, 2H), 1.74−1.88 (m, 3H), 1.97 (dddd, *J* = 3.4, 3.3, 3.2, 3.0 Hz, 1H, H(5)*eq*), 2.43 (dddd, *J* = 13.0, 4.5, 3.4, 2.4 Hz, 1H, H(9)*eq*), 3.84 (m, 1H, H(1)*eq*), 9.68 (s, 1H, H(12)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (C(11)H_3), 19.1 (C(10)H_3), 26.7 (CH_2), 28.8 (CH_2), 29.3 (CH_2), 31.8 (C(5)H), 35.5 (C(8)H), 79.4 (C(1)H), 87.8 (C(4)), 202.6 (C(12)H=O); IR (neat) ν 2956 (s), 2928 (s), 2869 (s), 2809 (m), 2708 (m), 1732 (s), 1456 (m), 1376 (m), 1131 (m), 1097 (m), 1042 (m) cm^{-1}; MS (*m*/*z*) 169.09 (26), 167.06 (12), 152.99 (57), 137.05 (100), 135.05 (33), 108.95(88); HRMS calcd for $C_{10}H_{17}O_3$ [MH^+] 185.1178, found 185.1185.

Mukaiyama Aldol Addition of Enol Ether 35 to Aldehyde 7. Aldehyde **7** (16 mg; 0.087 mmol) and enol ether **35** (3 equiv; 64 mg; 0.26 mmol) were dissolved in dry dichloromethane (0.5 mL) under argon and cooled to −78 °C. A 1.2 M solution of $TiCl_4$ in dichloromethane (3 equiv; 0.2 mL; 0.26 mmol) was added dropwise over 15 min to give a deep red solution. The reaction mixture was stirred at −78 °C for 4 h and quenched by addition of 0.5 M K_2CO_3 (1 mL) and an additional 2 mL of dichloromethane. After 10 min, the temperature was increased to 0 °C and the reaction mixture was stirred at this temperature for 1 h. Water (5 mL) was added, and the mixture was extracted with 33% ethyl acetate/hexane (2 × 25 mL). The combined extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. TLC analysis of the crude residue revealed the presence of three endoperoxidic products. To the crude residue was added a 0.2 M solution of HCl in methanol (3 mL). The reaction mixture was stirred for 2 h. and then neutralized by addition of $NaHCO_3$ (pH = 8). The solvent was removed under reduced pressure. The residue was dried azeotropically with toluene and purified by flash chromatography (gradient: 10% to 30% ethyl acetate/hexane) to afford 1-[(1*S*,2*R*,5*S*,6*R*)-2,6-dimethyl-3,4-dioxabicyclo-[3.3.1]non-2-yl]-1,4-dihydroxy-4-methyl-3-pentanone (**36**) as an oil (17.5 mg; 70% yield): R_f = 0.18 (30% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$, major isomer) δ 1.08 (s, 3H, Me-(11)), 1.09 (d, *J* = 6.6 Hz, 3H, Me(10)), 1.41 (s, 3H, Me(16)), 1.42 (s, 3H, Me(16′)), 1.47 (ddd, *J* = 13.4, 2.9, 1.7 Hz, 1H, H(9)-*ax*), 1.63−1.73 (m, 2H, H(6) + H(7)), 1.84 (m, 1H, H(8)*ax*), 1.89−2.06 (m, 2H, H(6) + H(7)), 2.11 (dddd, *J* = 3.7, 3.7, 3.2, 2.9, 1H, H(5)*eq*), 2.51 (dddd, *J* = 13.4, 6.8, 3.7, 3.7 Hz, 1H, H(9)*eq*), 2.56 (dd, *J* = 17.8, 10.2 Hz, 1H, H(13)), 2.98 (d, *J* =

3.3 Hz, 1H, OH), 3.10 (dd, J = 17.8, 1.6 Hz, 1H, H(13′)), 3.62 (s, 1H, OH), 3.82 (m, 1H, H(1)*eq*), 4.91 (ddd, J = 10.2, 3.3, 1.6 Hz; 1H, H(12)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (C(11)H_3), 18.6 (C(10)H_3), 26.5(C(5)H), 26.6 (C(16)H_3), 27.03 (C(16′)H_3), 27.09 (C(6)H_2), 29.2 (C(9)H_2), 29.7 (C(7)H_2), 35.6 (C(8)H), 36.6 (C(13)H_2), 67.0 (C(12)H), 79.4 (C(1)H), 83.4 (C(4)), 217.0 (C(14)=O); MS (*m/z*) 287.18 (MH^+, 12), 269.17 (15), 157.11 (23), 139.11 (100), 113.06 (67), 95.04 (81); HRMS calcd for $C_{15}H_{27}O_5$ [MH^+] 287.1858, found 287.1840.

Mukaiyama Aldol Addition of Enol Ether 35 to Aldehyde 7 and Treatment with Pyridine at 0 °C. Mukaiyama aldol addition of enol ether **35** (4 equiv; 187 mg; 0.76 mmol) to aldehyde **7** (35 mg; 0.190 mmol) was carried out as described above, but after the reaction mixture was stirred for 4 h at −78 °C, a solution of pyridine (18 equiv; 0.4 mL; 5.6 mmol) in dichloromethane (1 mL) was added. The resulting mixture was stirred at −78 °C for 10 min and then at 0 °C for 10 min. The reaction mixture was poured into a solution of 2.5% $NaHCO_3$ (30 mL) with dichloromethane (2 × 3 mL) to afford an heterogeneous mixture. Dichloromethane (5 mL), ether (20 mL), and hexane (20 mL) were added. The phases were separated, and the water phase was extracted with ether (20 mL). The combined organic extracts were filtered through Celite and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Three flash chromatographies (first, gradient 0% to 5% to 10% ethyl acetate/hexane; second, 4% ethyl acetate/hexane; third, 3% ethyl acetate/hexane) afforded impure **37** (36 mg) and impure **39** (29 mg) and pure aldol addition product **38** (18.5 mg; 27% yield) as a colorless oil. The yield of **39** was confirmed by conversion into α,β-unsaturated ketone **9** (13.5 mg; 27% yield from aldehyde **7**) as described below. The yield of **37** was determined by conversion into aldol addition product **36** (8 mg; 15% yield from aldehyde **7**) by reaction with HCl in methanol as described above.

Mukaiyama Aldol Addition of Enol Ether 35 to Aldehyde 7 and Treatment with Pyridine at 21 °C. Mukaiyama aldol addition of enol ether **35** (4 equiv; 171 mg; 0.695 mmol) to aldehyde **7** (32 mg; 0.174 mmol) was carried out as described above, but after the addition of pyridine (32 equiv; 0.4 mL; 5.6 mmol) the reaction was allow to warm to room temperature over 1 h. The reaction mixture was stirred at room temperature for 1 h and then poured into a 2.5% solution of $NaHCO_3$ (30 mL). The resulting heterogeneous mixture was extracted with dichloromethane/ether/hexane (1:1:1; 4 × 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered through Celite, and concentrated at reduced pressure to afford an oil (24.7 mg) containing α,β-unsaturated ketone **39** corresponding to 20% yield and aldol addition product **38** corresponding to 22% yield as determined from the ^{1}H NMR spectra.

Mukaiyama Aldol Addition of Enol Ether 35 to Aldehyde 7 and Treatment with Pyridine at −40 to 0 °C. Mukaiyama aldol addition of enol ether **35** (4 equiv; 238 mg; 0.966 mmol) to aldehyde **7** (44.5 mg; 0.242 mmol) was carried out as described above, but after the addition of pyridine (23 equiv; 0.4 mL; 5.6 mmol) the reaction was stirred at −78 °C for 1.5 h (no reaction observed by TLC), at −40 to −20 °C for 2 h. (no reaction observed by TLC), at −20 to −10 °C for 2.5 h, and at 0 °C for 2 h and kept at this temperature for 1 h. The reaction mixture was poured into saturated $NaHCO_3$ (30 mL). The resulting heterogeneous mixture was extracted with dichloromethane/ether/hexane (1:1:1; 8 × 25 mL) and dichloromethane (8 × 15 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. Flash chromatography (gradient 6% to 30% ethyl acetate/hexane) afforded α,β-unsaturated ketone **39** (16 mg; 20% yield) as a white solid.

One-Pot Procedure for Mukaiyama Aldol Addition of Enol Ether 35 to Aldehyde 7 and Subsequent Dehydration *in Situ* with Pyridine at −20 °C. Aldehyde **7** (63 mg; 0.34 mmol) and enol ether **35** (5 equiv; 420 mg; 1.7 mmol) were dissolved in dry dichloromethane (1.5 mL) under argon and cooled to −78 °C. A 2.7 M solution of $TiCl_4$ in dichloromethane (4 equiv; 0.5 mL; 1.36 mmol) was added dropwise over 15 min to give a deep red solution. The reaction mixture was stirred at −78 °C for 4 h, at which time a solution of pyridine (21 equiv; 0.5 mL; 7 mmol) in dichloromethane (1.6 mL) was added. The resulting solution was heated to −20 °C over 40 min and stirred between −30 and −20 °C for an additional 11 h. The reaction mixture was poured into saturated $NaHCO_3$ (45 mL). The resulting heterogeneous mixture was extracted with dichloromethane/ether/hexane (1:1:1; 7 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated at reduced pressure. Flash chromatography (gradient: 6% to 13% to 30% ethyl acetate/hexane) afforded 19.3 mg (13% yield) of bis-TMS aldol product (**37**) as a clear oil and α,β-unsaturated ketone **39** (81 mg; 70% yield) as a white solid.

1-[(1*S*,2*S*,5*S*,6*R*)-2,6-Dimethyl-3,4-dioxabicyclo[3.3.1]-non-2-yl]-4-methyl-1,4-bis(trimethylsilyloxy)-3-pentanone (37): colorless oil; R_f = 0.82 (10% ethyl acetate/hexane); $[\alpha]^{20}_D$ = 23.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.09 (s, 9H, 3 × CH_3Si), 0.16 (s, 9H, 3 × CH_3Si), 1.05 (s, 3H, Me(11)), 1.07 (d, J = 6.6 Hz, 3H, Me(10)), 1.32 (s, 3H, Me(16)), 1.35 (s, 3H, Me(16′)), 1.44 (ddd, J = 13.1, 2.8, 1.7 Hz, 1H, H(9)*ax*), 1.55−2.06 (m, 6H), 2.56 (dddd, J = 13.0, 6.5, 4.1, 3.7 Hz, 1H, H(9)*eq*), 2.86 (dd, J = 18.9, 8.4 Hz, 1H, H(13)), 3.02 (dd, J = 18.9, 2.1 Hz, 1H, H(13′)), 3.80 (m, 1H, H(1)*eq*), 5.05 (dd, J = 8.4, 2.1 Hz; 1H, H(12)); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 0.8 (3 × CH_3Si), 2.4 (3 × CH_3Si), 16.3 (C(11)H_3), 18.6 (C(10)H_3), 27.1 (C(5)H + C(16)H_3), 27.2 (CH_2), 27.3 (C(16′)-H_3), 29.2 (CH_2), 29.7 (CH_2), 35.6 (C(8)H), 38.7 (C(13)H_2), 67.4 (C(12)H), 78.9 (C(1)H), 80.1 (C(15)), 84.2 (C(4)), 214.3 (C(14)=O); IR (neat) ν 2945 (s), 2930 (s), 2866 (m), 1721 (s), 1456 (m), 1375 (m), 1254 (s) 1108 (s), 1045 (s); MS (*m/z*) 431.26 (MH^+, 5), 341.22 (21), 325.19 (33), 185.10 (19), 156.97(15), 139.05 (22), 131.09 (100), 95.07 (13); HRMS calcd for $C_{21}H_{43}O_5Si_2$ [MH^+] 431.2649, found 431.2641.

1-[(1*S*,2*S*,5*S*,6*R*)-2,6-Dimethyl-3,4-dioxabicyclo[3.3.1]-non-2-yl]-1-hydroxy-4-trimethylsilyloxy-4-methyl-3-pentanone (38): colorless oil; R_f = 0.15 (10% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$, major isomer) δ 0.16 (s, 9H, 3 × CH_3Si), 1.05 (s, 3H, Me(11)), 1.08 (d, J = 6.8 Hz, 3H, Me(10)), 1.35 (s, 3H, Me(16)), 1.36 (s, 3H, Me(16′)), 1.44 (ddd, J = 13.3, 2.9, 1.7 Hz, 1H, H(9)*ax*), 1.67 (m, 2H, H(6) + H(7)), 1.82 (m, 1H, H(8)*ax*), 1.89−2.06 (m, 2H, H(6′) + H(7′)), 2.11 (m, 1H, H(5)*eq*), 2.56 (dddd, J = 13.3, 6.6, 4.1, 3.9 Hz, 1H, H(9)*eq*), 2.69 (dd, J = 18.2, 10.5 Hz, 1H, H(13)), 3.08 (d, J = 3.5 Hz, 1H, OH), 3.14 (dd, J = 18.2, 1.6 Hz, 1H, H(13′)), 3.80 (m, 1H, H(1)*eq*), 4.84 (ddd, J = 10.4, 3.5, 1.6 Hz, 1H, H(12)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.3 (3 × CH_3Si), 15.9 (C(11)H_3), 18.6 (C(10)H_3), 27.0 (C(5)H), 27.1 (C(6)H_2), 27.2 (C(16)H_3), 27.3 (C(16′)H_3), 29.3 (C(9)H_2), 29.7 (C(7)H_2), 35.8 (C(8)H), 37.2 (C(13)H_2), 66.9 (C(12)H), 79.3 (C(1)H), 80.3 (C(15)), 83.5 (C(4)), 217.7 (C(14)=O, ketone); MS (*m/z*) 359.22 (MH^+, 8), 341.22 (21), 325.19 (20), 156.97(15), 139.05 (22), 131.09 (100), 95.07 (13); HRMS calcd for $C_{18}H_{34}O_5Si$ [MH^+] 359.2254, found 359.2230.

(*E*)-1-[(1*S*,2*S*,5*S*,6*R*)-2,6-Dimethyl-3,4-dioxabicyclo[3.3.1]-non-2-yl]-4-methyl-4-trimethylsilyloxy-1-penten-3-one (39): white solid; mp 45−47 °C; R_f = 0.46 (10% ethyl acetate/hexane); $[\alpha]^{20}_D$ =114.3 (*c* 1.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 9H, 3 × CH_3Si), 1.12 (d, J = 6.7 Hz, 3H, Me(10)), 1.23 (s, 3H, Me(11)), 1.37 (s, 3H, Me(16)), 1.38 (s, 3H, Me(16′)), 1.48 (ddd, J = 12.8, 3.3, 1.9 Hz, 1H, H(9)*ax*), 1.62−1.73 (m, 2H, H(6) + H(7)), 1.76 (dddd, J = 2.9, 2.9, 2.5, 2.5 Hz, 1H, H(5)*eq*), 1.82 (m, 1H, H(8)*ax*), 1.98−2.08 (m, 2H, H(6′) + H(7′)), 2.19 (dddd, J = 12.8, 5.9, 3.8 3.2 Hz, 1H, H(9)*eq*), 3.79 (m, 1H, H(1)*eq*), 7.02 and 7.05 (AB quartet, J = 16.0 Hz, 2H, H(12) + H(13)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.3 (3 × CH_3Si), 18.6 (C(10)H_3), 23.5 (C(11)H_3), 26.3 (CH_2), 26.9 (C(16)-H_3), 27.1 (C(16′)H_3), 29.4 (CH_2), 30.5 (CH_2), 32.0 (C(5)H), 35.4 (C(8)H), 79.1 (C(15)), 79.3 (C(1)H), 83.8 (C(4)), 123.4 (=C(13)H), 150.7 (=C(12)H), 202.9 (C(14)=O); IR (KBr) ν 2995 (w), 2974 (w), 2974 (m), 2955 (s), 2894 (m), 2870 (m), 1693 (s), 1627 (s), 1450 (m), 1374 (m), 1252 (s) 1044 (s) cm^{-1}; MS (*m/z*)

341.22 (MH^+, 36), 325.19 (33), 185.10 (19), 131.09 (100); HRMS calcd for $C_{18}H_{33}O_4Si$ [MH^+] 341.2148, found 341.2159.

(*E*)-1-[(1*S*,2*S*,5*S*,6*R*)-2,6-Dimethyl-3,4-dioxabicyclo[3.3.1]-non-2-yl]-4-hydroxy-4-methyl-1-penten-3-one (9). To a solution of α,β-unsaturated ketone **39** (30.5 mg; 0.089 mmol) in acetonitrile at 0 °C was added 1 mL of 2% HF in acetonitrile and the reaction mixture stirred for 25 min. The solution was poured into saturated $NaHCO_3$ (30 mL) and extracted with dichloromethane (6 × 15 mL). The organic extract was dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (20% ethyl acetate/hexane) afforded the title compound **9** (22.9 mg; 95% yield) as a clear oil: $R_f = 0.25$ (20% ethyl acetate/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, J = 6.8 Hz, 3H, Me(10)), 1.24 (s, 3H, Me(11)), 1.40 (s, 3H, Me-(16)), 1.42 (s, 3H, Me(16′)), 1.50 (ddd, J = 12.9, 3.2, 2.0 Hz, 1H, H(9)*ax*), 1.63−1.73 (m, 2H, H(6) + H(7)), 1.75 (m, 1H, H(5)-*eq*) 1.83 (m, 1H, H(8)*ax*), 1.97−2.09 (m, 2H, H(6′) + H(7′)), 2.19 (dddd, J = 12.9, 6.1, 3.1, 3.1 Hz, 1H, H(9)*eq*), 3.82 (m, 1H, H(1)*eq*), 3.97 (s, 1 OH), 6.83 (d, J = 15.5 Hz, 1H, H(13)), 7.08 (d, J = 15.5 Hz, 1H, H(12)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (C(10)H_3), 23.5 (C(11)H_3), 26.20 (C(6)H_2), 26.20 (C(16)-H_3), 26.24 (C(16′)H_3), 29.4 (C(7)H_2), 30.6 (C(9)H_2), 31.9 (C(5)H), 35.4 (C(8)H), 75.5 (C(15)), 79.6 (C(1)H), 83.9 (C(4)), 122.0 (=C(13)H), 152.4 (=C(12)H), 202.9 (C(14)=O); IR (neat) ν 3476 (br s), 2953 (s), 2930 (s), 2867 (s), 1691 (s), 1628 (s), 1453 (m), 1368 (m), 1283(s), 1066 (s) cm^{-1}; MS (*m/z*) 269.18 (MH^+, 14), 168.98 (23), 139.10 (47), 110.98 (39), 98.04 (87), 95.09 (100); HRMS calcd for $C_{15}H_{25}O_4$ [MH^+] 269.1753, found 269.1780.

Silylation of α,β-Unsaturated Ketone 9 To Afford α,β-Unsaturated Ketone 39. To a solution of α,β-unsaturated ketone **9** (33.5 mg; 0.125 mmol) in dichloromethane (2 mL) was added 2,6-lutidine (2 equiv; 0.03 mL; 0.25 mmol), and the solution was cooled to −30 °C. Trimethylsilyl triflate (1.5 equiv; 0.034 mL; 0.187 mmol) was added dropwise over 5 min. The reaction mixture was allowed to heat up to 0 °C over 30 min and stirred at this temperature for 3 h. The reaction mixture was poured into water (20 mL) and extracted with dichloromethane (90 mL + 2 ×10 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. Flash chromatography (10% ethyl acetate/hexane) afforded α,β-unsaturated ketone **39** (41 mg; 97% yield) as a white solid. Analytical data as described above.

Reduction of α,β-Unsaturated Ketone 9 by Sodium Borohydride/Europium(III) Chloride. α,β-Unsaturated ketone **9** (29 mg; 0.109 mmol) and europium(III) chloride (1 equiv; 28 mg; 0.109 mmol) were dissolved in dry ethanol (3 mL), and the solution was cooled to 0 °C. $NaBH_4$ (1.5 equiv; 7 mg; 0.18 mmol) was added in three portions and the reaction mixture stirred for 30 min. HCl (0.1 M, 10 mL) was added, and stirring was continued for 5 min. The solution was extracted with dichloromethane (6 × 15 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (35 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (50% ethyl acetate/hexane) afforded a viscous oil containing a 45:55 mixture of yingzhaosu A (**1**) and its C(14)-epimer **40** (28 mg; 95% combined yield) as judged from the H(12) signals in the ^1H NMR spectrum, R_f = 0.13 (30% ethyl acetate/hexane). For analytical data, see below.

Reduction of α,β-Unsaturated Ketone 9 by DIBAL-H. Ketone **9** (22.9 mg; 0.0853 mmol) was dissolved in dry THF (2 mL) and the solution cooled to −78 °C. A 0.26 mM solution of DIBAL-H in THF (1.5 equiv; 0.5 mL; 0.129 mmol) was added. The reaction mixture was stirred for 1.5 h, and then an additional portion of 0.26 mM DIBAL-H solution (1.5 equiv; 0.5 mL; 0.129 mmol) was added. After the mixture was stirred for 2 h, a third portion (1.5 equiv; 0.5 mL; 0.129 mmol) was added. The reaction mixture was stirred for 1 h at −78 °C and 2.5 h at −50 °C and then quenched by the addition of 0.1 mL of acetic acid. The resulting mixture was poured into saturated $NaHCO_3$ (35 mL) resulting in a heterogeneous mixture. The heterogeneous mixture was extracted with dichloromethane/hexane/ether (1:1:1; 4 × 35 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (50% ethyl acetate/hexane) afforded recovered α,β-unsaturated ketone **9** (10.5 mg; 44% yield) and a viscous oil containing a 45:55 mixture of yingzhaosu A (**1**) and its C(14)-epimer **40** (13 mg; 99% yield based on recovered ketone **9**) as judged from the H(12) signals in the ^1H NMR spectrum. For analytical data, see below.

Reduction of α,β-Unsaturated Ketone 39 by *R*-BINAL-H. A solution of *R*-BINAL-H **41** (2 equiv; 0.2 mmol) in THF (1.5 mL) was freshly prepared according to Noyori's procedure[41] and cooled to −78 °C. A solution of α,β-unsaturated ketone **39** (34 mg; 0.10 mmol) in THF (1 mL) was added by cannula. The reaction mixture was stirred for 3 h at −78 °C (no reaction could be observed by TLC) and 7 h at −50 to −60 °C. The reaction mixture was poured into cold saturated $NaHCO_3$ (30 mL) resulting in a heterogeneous mixture. The heterogeneous mixture was extracted with dichloromethane (7 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (50% ethyl acetate/hexane) afforded α,β-unsaturated ketone **39** (8.4 mg; 25% yield) and a brownish viscous oil containing crude TMS-protected yingzhaosu A (**1**) and C(14)-epimer **40**. The brown oil was treated with a 2% HF/ethanol (3 mL) for 15 min. The resulting solution was poured into saturated $NaHCO_3$ (40 mL) and extracted with dichloromethane (6 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (50% ethyl acetate/hexane) afforded a colorless oil (10.2 mg; 50% yield based on recovered α,β-unsaturated ketone **9**, 2 steps) containing yingzhaosu A (**1**) and its C(14)-epimer **40** in a 55:45 ratio (as judged from the H(12) signals in the ^1H NMR spectrum).

Reduction of α,β-Unsaturated Ketone 39 by *S*-CBS Catalyst 42a/Catecholborane. A solution of freshly prepared[49] *S*-CBS catalyst **42a** (1.0 equiv; 0.1 mmol) in toluene/dichloromethane (1:1; 1 mL) was cannulated into a vial fitted with a sidearm and a flo-stopcock under argon. A solution of 0.264 M catecholborane solution in dichloromethane (1.3 equiv; 0.5 mL; 0.13 mmol) was added via a syringe. The resulting solution was aged for 30 min and then cooled to −78 °C. Ketone **39** (34 mg; 0.1 mmol) was dissolved in dry dichloromethane (1.5 mL) and cannulated into the reaction vessel. The vessel was closed and kept at −20 °C for 16 h. At this time the vessel was cooled to −78 °C. The reaction was quenched by the addition of methanol (0.3 mL). A 40% solution of HF in water (0.1 mL) was added, the cooling bath removed, and the reaction stirred at room temperature for 1 h. The reaction mixture was poured into a 0.04 M solution of HCl (45 mL) and extracted with dichloromethane (6 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure. Flash chromatography (gradient 20% to 30% to 50% ethyl acetate/hexane) afforded α,β-unsaturated ketone **9** (13.3 mg; 49% yield) as a colorless oil and a mixture of yingzhaosu A (**1**) and its C(14)-epimer **40** (13.2 mg; 97% yield based on recovered α,β-unsaturated ketone **9**; **1**:**40** ca. 66:33 as judged from the H(12) signals in the ^1H NMR spectrum) as a colorless oil.

Reduction of α,β-Unsaturated Ketone 39 by *S*-CBS Catalyst 42a/Borane in Dichloromethane. A solution of freshly prepared[49] *S*-CBS catalyst **42a** (1.0 equiv; 0.1 mmol) in toluene/dichloromethane (1:1; 1 mL) was cannulated into a vial fitted with a sidearm and a flo-stopcock under argon. A solution of 1 M borane-THF solution (1.1 equiv; 0.11 mL; 0.11 mmol) was added via a syringe. The resulting solution was aged for 30 min and then cooled to −78 °C. Ketone **39** (34 mg; 0.1 mmol) was dissolved in dry dichloromethane (0.5) and cannulated into the reaction vessel with additional dichloromethane (0.5 mL). The vessel closed, and then was heated to

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−40 °C and kept at this temperature for 16 h. The reaction was quenched by the addition of methanol (0.5 mL). A 40% solution of HF in water (0.15 mL) was added and the reaction heated to room temperature. The reaction mixture was stirred at room temperature for 1 h and then poured into a 0.04 M solution of HCl (45 mL). The phases were separated, and the water phase was extracted with dichloromethane (6 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure. Flash chromatography (gradient 20% to 30% to 50% ethyl acetate/hexane) afforded α,β-unsaturated ketone **9** (8.1 mg; 30% yield) and a mixture of yingzhaosu A (**1**) and its C(14)-epimer **40** (17.1 mg; 90% yield based on recovered α,β-unsaturated ketone **9**; **1**:**40** ca. 16:84 as judged from the H(12) signals in the ^{1}H NMR spectrum) as a colorless oil that solidified on standing.

Reduction of α,β-Unsaturated Ketone 39 by *R*-CBS Catalyst 42b/Borane in THF. A solution of freshly prepared[49] *R*-CBS catalyst **42b** (1.2 equiv; 65.2 mg; 0.240 mmol) in THF (3 mL) was cannulated into a vial fitted with a sidearm and a flo-stopcock under argon. A 1 M solution of borane−THF complex (1.2 equiv; 0.24 mL; 0.24 mmol) was added via a syringe. The resulting solution was aged for 30 min and then cooled to −78 °C. Ketone **39** (68 mg; 0.200 mmol) was dissolved in dry THF (3 mL) and cannulated into the reaction vessel. The vessel was closed and kept at − 55 °C for 28 h. At this time the vessel was cooled to −78 °C. The reaction was quenched by the addition of 1 mL of methanol and poured into 45 mL of phosphate buffer (pH = 8). The mixture was stirred for 30 min at room temperature and then extracted with 50% dichloromethane/hexane (6 × 20 mL). The extracts were combined, and the solvent was removed under reduced pressure. A 2% solution of HF in ethanol was added to the residue and the resulting reaction mixture stirred for 15 min. The solution was poured into saturated $NaHCO_3$ (40 mL) and extracted with dichloromethane (6 × 25 mL). The organic combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (50% ethyl acetate/hexane) afforded 38 mg (71% yield) of a viscous oil that solidified on standing. This mixture contained a 89:11 mixture of yingzhaosu A (**1**) and its C(14)-epimer **40** as judged from the H(12) signals in the ^{1}H NMR spectrum. The two diastereoisomers were separated by several recrystallizations from 25% *tert*-butyl methyl ether/pentane. **Recovery of Diphenylpyrrolidin-2-ylmethanol.** The two water phases mentioned above were combined (total 80 mL) and basified by the addition of solid sodium hydroxide (ca. 4.0 g, pH = 13) and extracted with toluene (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to afford diphenylpyrrolidin-2-ylmethanol (47.5 mg) as an oil that was crystallized from hexane.

Reduction of α,β-Unsaturated Ketone 39 by *S*-CBS Catalyst 42a/Borane in THF. The reaction was carried out according to the procedure described above for reduction of α,β-unsaturated ketone **39** with the *R*-CBS catalyst **42b**. Reduction of 38 mg (0.112 mmol) of α,β-unsaturated ketone **39** afforded 21.8 mg (72% yield) of a mixture of **40** and yingzhaosu A (**1**) as an oil that solidified on standing. This mixture contained a 11:89 mixture of yingzhaosu A (**1**) and its C(14)-epimer **40** as judged from the H(12) signals in the ^{1}H NMR spectrum. The two diastereoisomers were separated by fractional recrystallization from 10% ethyl acetate/hexane.

(5*S*)-5-{(*E*)-2-[(2*S*,5*S*,6*R*)-2,6-Dimethyl-3,4-dioxabicyclo-[3.3.1]non-2-yl]-1-ethenyl}-4,4-dimethyl-1,3-dioxolan-2-one (43) and (5*R*)-5-{(*E*)-2-[(2*S*,5*S*,6*R*)-2,6-Dimethyl-3,4-dioxabicyclo[3.3.1]non-2-yl]-1-ethenyl}-4,4-dimethyl-1,3-dioxolan-2-one (44). A mixture of yingzhaosu A (**1**) and its C(14)-epimer **40** (40 mg; 0.148 mmol; **1**:**40** ca. 45:55) was dissolved in dry THF (2 mL). *N*,*N*′-Carbonyldiimidazole (120 mg; 0.740 mmol; 5 equiv) was added, and the reaction mixture was heated and stirred at 50−60 °C for 2 h. Water (15 mL) was added and the reaction mixture stirred at room temperature for 2h. An additional 7 mL of water was added and the resulting solution extracted with 25% ethyl acetate/hexane (7 × 15 mL). The combined extract was dried (Na_2SO_4) and concentrated at reduced pressure. Flash chromatography (20% ethyl acetate/hexane) afforded a colorless oil (39.5 mg; 90%) containing a mixture of the diastereomeric carbonates **43** and **44** (ca. 45:55). The carbonates were separated by semipreparative direct-phase HPLC (15% ethyl acetate/hexane).

(5*S*)-5-{(*E*)-2-[(2*S*,5*S*,6*R*)-2,6-Dimethyl-3,4-dioxabicyclo-[3.3.1]non-2-yl]-1-ethenyl}-4,4-dimethyl-1,3-dioxolan-2-one (43): viscous oil; R_f = 0.37 (25% ethyl acetate/hexane); t_R =20.99 min. (15% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.8 Hz, 3H, Me(10)), 1.21 (s, 3H, Me-(11)), 1.34 (br s, 3H, Me(16)), 1.48 (ddd, *J* = 12.8, 3.0, 1.9 Hz, 1H, H(9)*ax*), 1.52 (br s, 3H, Me(16′)), 1.62−1.74 (m, 3H, H(5)-*eq* + H(6) + H(7)), 1.76−1.86 (m, 1H, H(8)*ax*), 1.97−2.08 (m, 2H, H(6′) + H(7′)), 2.21 (dddd, *J* = 12.8, 3.8, 2.8, 2.5 Hz, 1H, H(9)*eq*), 3.80 (m, 1H, H(1)*eq*), 4.77 (dd, *J* = 7.0, 1.2 Hz, 1H, H(14)), 5.82 (dd, *J* = 15.8, 7.0 Hz, 1H, H(13)), 6.06 (dd, *J* = 15.8, 1.2 Hz, 1H, H(12)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 ($C(10)H_3$), 22.3 ($C(16)H_3$), 24.1 ($C(16')H_3$), 25.9 ($C(11)H_3$), 26.4 ($C(6)H_2$), 29.4 ($C(7)H_2$), 30.4 ($C(9)H_2$), 32.2 (C(5)H), 35.5 (C(8)H), 79.5 (C(1)H), 83.3 (C(4)), 84.5 (C(15)), 85.4 (C(14)H), 121.5 (=C(13)H), 140.2 (=C(12)H), 153.9 (O_2C=O); IR(KBr) ν 2983 (m), 2961 (m), 2951 (m), 2928 (m) 2904 (w), 2867 (m), 2860 (w), 1787 (s), 1450 (m), 1395 (m), 1379 (m) 1368 (w), 1352 (m), 1334 (w), 1236 (s), 1268 (m), 1122(m), 1104 (m), 1093 (m), 1049 (m), 1024 (s), 973 (m); MS (*m*/*z*) 297.19 (MH^+, 8), 280.98 (50), 268.98 (35), 250.98 (23), 242.99 (28), 230.99 (35), 220.00 (28), 218.98 (44), 201.16 (30), 185.08 (78), 180.98 (43), 168.99 (100), 141.10 (32), 130.99 (89), 126.03 (28), 123.08 (65), 118.99 (94), 113.09 (64), 109.06 (38), 95.09 (88); HRMS calcd for $C_{15}H_{25}O_4$ [MH^+] 297.1702, found 297.1688.

(5*R*)-5-{(*E*)-2-[(2*S*,5*S*,6*R*)-2,6-Dimethyl-3,4-dioxabicyclo-[3.3.1]non-2-yl]-1-ethenyl}-4,4-dimethyl-1,3-dioxolan-2-one (44): white solid; R_f = 0.40 (25% ethyl acetate/hexane); t_R =19.08 min. (15% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.8 Hz, 3H, Me(10)), 1.20 (s, 3H, Me-(11)), 1.36 (br s, 3H, Me(16)), 1.48 (ddd, *J* = 12.8, 3.0, 1.9 Hz, 1H, H(9)*ax*), 1.53 (br s, 3H, Me(16′)), 1.62−1.74 (m, 3H, H(5)-*eq* + H(6) + H(7)), 1.76−1.86 (m, 1H, H(8)*ax*), 1.97−2.08 (m, 2H, H(6′) + H(7′)), 2.21 (dddd, *J* = 12.8, 3.7, 2.9, 2.5 Hz, 1H, H(9)*eq*), 3.80 (m, 1H, H(1)*eq*), 4.76 (dd, *J* = 6.2, 1.2 Hz, 1H, H(14)), 5.83 (dd, *J* = 15.8, 6.2 Hz, 1H, H(13)), 6.01 (dd, *J* = 15.8, 1.2 Hz, 1H, H(12)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 ($C(10)H_3$), 22.5 ($C(11)H_3$), 24.1 ($C(16)H_3$), 25.9 ($C(16')H_3$), 26.4 (CH_2), 29.4 (CH_2), 30.3 (CH_2), 32.1 (C(5)H), 35.5 (C(8)H), 79.5 (C(1)H), 83.4 (C(4)), 84.5 (C(15)), 85.3 (C(14)H), 121.3 (=C(13)H), 140.5 (=C(12)H), 153.2 (O_2C=O); IR(KBr) ν 2991 (w), 2977 (w), 2959 (m), 2924 (m) 2866 (m), 2856 (m), 1791 (s), 1455 (m), 1447 (w), 1391 (w) 1381 (m), 1332 (w), 1279 (m), 1238 (m), 1100(m), 1025 (m); MS (*m*/*z*) 297.18 (MH^+, 19), 185.08 (88), 141.12 (28), 126.03 (50), 123.08 (59), 113.10 (57), 109.06 (36), 99.08 (32), 95.09 (100) 81.97 (52), 68.82 (50); HRMS calcd for $C_{15}H_{25}O_4$ [MH^+] 297.1702, found 297.1750.

Synthesis of Yingzhaosu A (1) from Carbonate 43. To a solution of carbonate **43** (14.1 mg; 0.048 mmol) in dry ether (1 mL) under argon at 0 °C was added 0.5 mL of a 0.095 M solution of $LiBH_4$ in ether (1 equiv; 0.048 mmol). The reaction mixture was stirred at 0 °C for 1 h, after which time an additional portion of 0.5 mL of the 0.095 M $LiBH_4$ solution was added. The reaction mixture was stirred for an additional 1 h at 0 °C, at which time 0.1 M HCl (10 mL) was added and the mixture stirred for 10 min. An additional 10 mL of water was added and the resulting solution extracted with dichloromethane (8 × 15 mL). The combined extract was washed with saturated $NaHCO_3$ (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (50% ethyl acetate/hexane) gave yingzhaosu A (**1**) as an oil (11.8 mg; 92%) which solidified on standing.

Synthesis of C(14)-Epiyingzhaosu A (40) from Carbonate 44. Reduction of carbonate **44** (17.1 mg; 0.058 mmol) was

carried out as described above to afford C(14)-epiyingzhaosu A (**40**) as an oil (14.7 mg; 94%) that solidified upon standing.

Yingzhaosu A (1): long, colorless cylindrical crystals; mp 94−94.5 °C (*tert*-butyl methyl ether/pentane; lit.[2a] mp 95−96 °C); R_f = 0.13 (30% ethyl acetate/hexane); $[\alpha]^{20}_D$ = 227.4 (*c* 1.30, $CHCl_3$) [lit.[2a] $[\alpha]^{25}_D$ = 224.0 ($CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, J = 6.8 Hz, 3H, Me(10)), 1.17 (br s, 3H, Me-(16)), 1.20 (s, 3H, Me(16′)), 1.25 (br s, 3H, Me(11)), 1.45 (ddd, J = 12.8, 3.2, 1.9 Hz, 1H, H(9)*ax*), 1.62−1.73 (m, 3H, H(5)*eq* + H(6) + H(7)), 1.76−1.84 (m, 1H, H(8)*ax*), 1.98−2.07 (m, 2H, H(6′) + H(7′)), 2.12 (br s, 1H, OH), 2.23 (br d, J = 3.8 Hz, 1H, OH), 2.30 (dddd, J = 12.8, 3.8, 2.9, 2.6 Hz, 1H, H(9)*eq*), 3.81 (m, 1H, H(1)*eq*), 3.97 (ddd, J = 7.0, 3.8, 1.0 Hz, H(14)), 5.82 (dd, J = 16.0, 7.0 Hz, 1H, H(13)), 5.97 (dd, J =16.0, J = 1.0 Hz, 1H, H(12)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (C(10)H_3), 23.7 (C(16)H_3), 24.3 (C(16′)H_3), 26.3 (C(11)H_3), 26.5 (C(6)H_2), 29.5 (C(7)H_2), 30.3 (C(9)H_2), 32.1 (C(5)H), 35.5 (C(8)H), 73.0 (C(15)), 79.4 (C(1)H + C(14)H), 83.4 (C(4)), 127.8 (=C(13)H), 138.4 (=C(12)H); IR (KBr) ν 3510 (m), 3356 (br s), 2975 (m), 2963 (m) 2935 (m), 2858 (m), 1457 (m), 1453 (w), 1374 (m), 1343 (w), 1169 (w), 1149 (w), 1090 (m) 985 (m) cm^{-1}; MS: (*m/z*) 253.18 ($MH^+ - H_2O$, 4), 230.99 (15), 219.15 (10), 219.0 (21), 212.14 (12), 195.15 (13), 177.13 (23), 168.99 (23), 141.09 (100), 139. 11 (25), 130.99 (42), 118.99 (48), 111.09 (38), 109.07 (42); HRMS calcd for $C_{15}H_{25}O_3$ [$MH^+ - H_2O$] 253.1804, found 253.1796;

Crystal Data. X-ray crystallographic data was collected on a Nonius KappaCCD diffractometer at Mo Kα (λ = 0.71073 Å); $C_{15}H_{26}O_4$, colorless, prism, 0.1 × 0.1 × 0.1 mm^3, orthorhombic, *P*2(1)2(1)2(1) (No. 19), a = 6.0030(12) Å, b = 9.981-(2) Å, c = 26.437(5) Å, from 20 degrees of data, T = 293(2) K, V = 1584.0(5) $Å^3$, Z = 4, Fw = 270.36, D_c = 1.134 $Mg{\cdot}m^{-3}$, μ = 0.080 mm^{-1}. Structure solved by direct methods and refined by full-matrix least-squares refinement based on F^2 with SHELXL-97. The final cycle of refinement based on F^2 gave an *R*-factor R = 0.042 for data with $I > 2\sigma(I)$ and R = 0.046 on all 1166 reflections with a goodness of fit of 1.041. Idealized hydrogen atoms were placed and refined in the riding mode.

C(14)-Epiyingzhaosu A (40): white solid; mp 88−89 °C (ethyl acetate/hexane; lit.[2a] mp 55−56 °C); R_f = 0.13 (30% ethyl acetate/hexane); $[\alpha]^{20}_D$ = 238.0 (*c* 0.896 $CHCl_3$) [lit.[2a] $[\alpha]^{25}_D$ = 234.0 ($CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, J = 6.8 Hz, 3H, Me(10)), 1.17 (br s, 3H, Me(16)), 1.21 (s, 3H, Me(16′)), 1.25 (br s, 3H, (Me(11)), 1.45 (ddd, J = 12.8, 3.1, 1.9 Hz, 1H, H(9)*ax*), 1.61−1.72 (m, 3H, H(5)*eq* + H(6) + H(7)), 1.75−1.85 (m, 1H, H(8)*ax*), 1.97−2.08 (m, 2H, H(6′) + H(7′)), 2.12 (br s, 1H, OH), 2.30 (dddd, J = 12.8, 3.5, 2.9, 2.6 Hz, 1H, H(9)*eq*), 2.32 (br d, J = 3.4 Hz, 1H, OH), 3.80 (m, 1H, H(1)*eq*), 3.97 (ddd, J = 6.7, 3.4, 1.1 Hz, 1H, H(14)), 5.81 (dd, J = 16.0, 6.7 Hz, 1H, H(13)), 5.99 (dd, J = 16.0, J = 1.1 Hz, 1H, H(12)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (C(10)H_3), 23.8 (C(16)H_3), 24.3 (C(16′)H_3), 26.4 (C(11)H_3), 26.5 (C(6)H_2), 29.5 (C(7)H_2), 30.3 (C(9)H_2), 32.3 (C(5)H), 35.5 (C(8)H), 73.0 (C(15)), 79.2 (C(14)H), 79.3 (C(1)H), 83.4 (C(4)), 127.8 (=C(13)H), 138.1 (=C(12)H); IR (KBr) ν 3548 (m), 3347 (br s), 2950 (m), 2941 (m) 2924 (m), 2867 (m), 1461 (m), 1446 (w), 1384 (m), 1367 (w), 1206 (w), 1152 (w), 1104 (w), 1052 (w), 1034 (w), 1001 (w) 973 (w) cm^{-1}; MS (*m/z*) 271.19 (MH^+, 5), 253.18 (MH^+, 41), 235.15 ($MH^+ - H_2O$, 19), 219.15 (28) 212.14 (48), 195.13 (27), 177.13 (38), 141.09 (84), 139.09 (100), 135.11 (28), 125.11 (44); HRMS calcd for $C_{15}H_{27}O4$ [MH^+] 271.1909, found 271.1892.

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Supporting Information Available: Copies of NMR spectra for all new compounds and X-ray structure data for yingzhaosu A (**1**). Additional procedures for model experiments as well as for the synthesis and characterization of compounds **32**−**34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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