groups with a dihedral angle of 60° between the two planes and in which both CO groups are *cisoid* (length of the Pt–Pt bond 2.584 Å).[7a] Other related, crystallographically characterized dinuclear platinum carbonyl species include $[\{PtCl(CO)(PtBu_2Ph)\}_2]$[7b] and $[\{Pt(C_6F_5)(CO)(PPh_3)\}_2]$,[7c] which have dihedral angles of 70.1° and 78.6°, and Pt–Pt distances of 2.628 and 2.599(Å), respectively. Preliminary reports have also appeared for $[\{PtCl(CO)(PPh_3)\}_2]$[8] and, in all cases, the carbonyl groups are *cis* and the two phosphanes are *trans* to the Pt–Pt bond.

It has been shown that there is no correlation of d(Pt–Pt) with ^1J(Pt,Pt′) in closely related dinuclear platinum complexes.[8] It is worth noting that ^1J(Pt,Pt′) for **1** is 550.9 Hz, while the values for $[\{PtCl_2(CO)\}_2]^{2-}$ (5250 Hz)[9] and $[\{PtCl(CO)(PPh_3)\}_2]$ (760 Hz)[8] are widely different, although other related coupling constants are similar (see Table 1 and refs. [8, 9]).

Prolonged evacuation of **1** results in disproportionation and formation of **2** through loss of CO [see Eq. (2)]. In this case, ^{13}C and ^{195}Pt NMR measurements on unenriched and 99% ^{13}CO-enriched **2** show that there are two magnetically equivalent carbonyl groups per platinum with no ^{195}Pt–^{195}Pt coupling; **2** is thus a monomer. We presently favor a square-planar platinum(II) center with two CO ligands in a *cis* configuration, consistent with both IR and Raman measurements; the CO stretching frequencies are close to those for *cis*-$[Pt(CO)_2(SO_3F)_2]$,[5b] but higher than those for *cis*-$[Pt(CO)_2Cl_2]$.[10] It is difficult to be sure whether the other two coordination sites on platinum are occupied by a bidentate SO_4^{2-} or by two monodentate SO_4^{2-}/HSO_4^- groups since it is impossible to obtain any useful IR or Raman data in the sulfato region. However, when **1** is in concentrated H_2SO_4, it seems more probable that the other two sites are occupied by monodentate HSO_4^- groups as recently found for silver(I).[11]

The discovery of **1** suggests that homoleptic cationic carbonyl complexes of late transition metals in low oxidation states can be formed in media which are less acidic than the superacids that have been used previously. We found that this unusual dinuclear platinum carbonyl complex, **1**, exhibits high catalytic activity for the carbonylation of olefins;[12] future studies will investigate the detailed reaction mechanism of this catalytic activity and attempts will be made to obtain **1** as a crystalline salt.

Experimental Section

Standard canula transfer techniques were used for all sample manipulations. NMR spectra were recorded in D_2SO_4 at room temperature on a Bruker AMX 200. The ^{13}C chemical shifts were referenced to external tetramethylsilane (TMS), and ^{195}Pt chemical shifts were referenced to 42.8 MHz at such a magnetic field that the protons in external TMS resonate at exactly 200 MHz. NMR simulations were carried out using gNMR 4.1 (Cherwell Scientific, Oxford, UK). Infrared spectra were obtained on thin films between two silicon discs on a JASCO FT/IR-230 spectrometer. Raman spectra were recorded on a Nicolet FT-Raman 960 spectrometer.

1: PtO_2 (2 mmol) in 96% H_2SO_4 (10 mL) was vigorously stirred for 2 weeks under ^{12}CO at constant pressure (1 atm), whereupon the dark colloidal suspension became colorless. The resulting solution is very moisture sensitive. Complex **1** with 99% ^{13}CO was prepared similarly.

2: The IR spectrum of **1** in 96% H_2SO_4 was monitored with time under evacuation (0.001 Torr). When the band for **1** (2174 cm^{-1} for ^{12}CO and 2126 cm^{-1} for ^{13}CO) had disappeared (ca. 1 d), nitrogen was admitted to the solution, which contained only **2** and a black colloidal precipitate of Pt metal. The solution of **2** was transferred under nitrogen by canula and used for all the spectroscopic measurements. This solution is indefinitely stable under a nitrogen atmosphere.

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Enantioselective Total Synthesis of Epothilone A Using Multifunctional Asymmetric Catalyses**

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Epothilones (see Scheme 1 for epothilones A (**1**) and B (**2**)) show potent antitumor activity by binding and stabilizing microtubules in the same way as taxol, and they are promising drug candidates. Epothilones A and B were isolated from the

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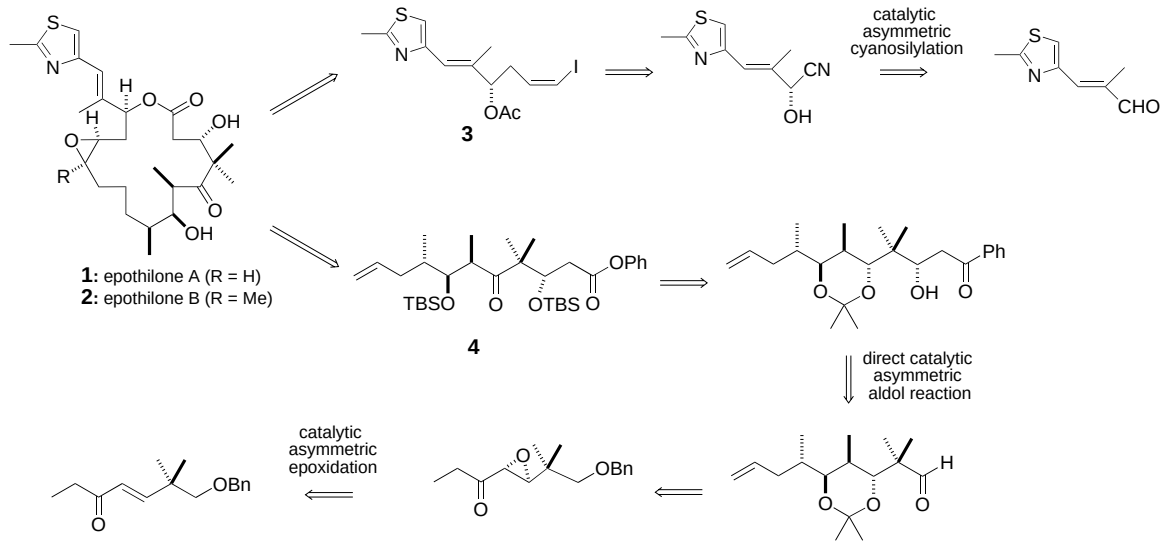


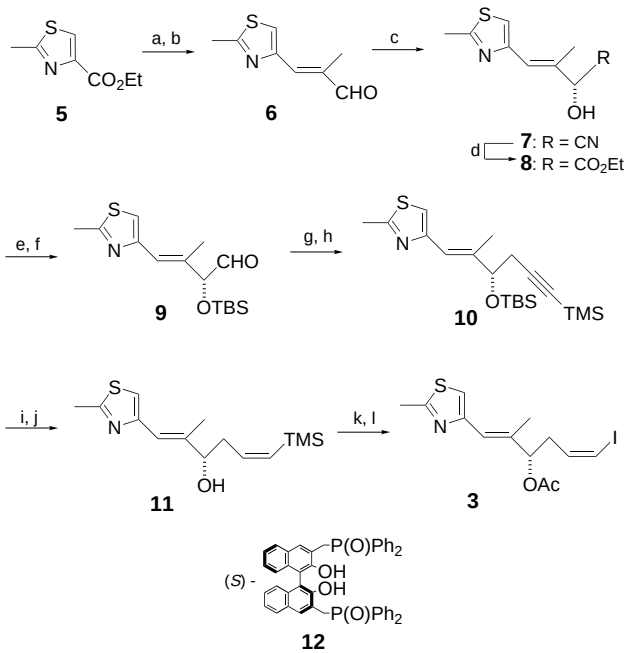
Scheme 1. Retrosynthetic analysis of **1**.

myxobacteria of the genus *Sorangium*, and their structures were determined by Höfle et al.[1] Highly efficient total syntheses of epothilones were disclosed by the research groups of Danishefsky, Nicolaou, and Schinzer,[2] but an enantioselective total synthesis using simple asymmetric catalysts has not been acheived.[3] Herein we report an enantioselective total synthesis of epothilone A (**1**) using multifunctional asymmetric catalyses for direct aldol reaction and cyanosilylation, demonstrating the usefulness of these reactions for the catalytic asymmetric synthesis of complex molecules.

Scheme 1 shows our retrosynthetic strategy. Epothilone A (**1**) was disconnected into two fragments, **3** and **4**. The 16-membered ring of **1** was expected to be constructed by Suzuki coupling of **3** and **4** followed by lactonization. The vinyl iodide **3** could be obtained by a catalytic asymmetric cyanosilylation controlled by a Lewis acid–Lewis base bifunctional catalyst.[4] The ester **4** could be synthesized by a catalytic asymmetric epoxidation and aldol reaction.[5, 6]

The known ester **5** was converted into aldehyde **6** in two steps for the synthesis of fragment **3** (Scheme 2).[2b] We then examined a catalytic asymmetric cyanosilylation of **6** using a Lewis acid–Lewis base bifunctional catalyst containing ligand **12** (>1-g scale).[4] With use of 10 mol% of the catalyst, cyanohydrin **7** was obtained in excellent yield and enantiomeric excess (97% yield, 99% *ee*) after acid workup.[7] Conversion of the cyanohydrin into the ester **8** by acidic ethanolysis followed by protection and reduction resulted in the aldehyde **9**. Addition of lithium acetylide to **9** afforded the alcohol product as a mixture of diastereomers, which was directly treated with methyl chloroformate to give the methyl carbonate. Reductive deoxygenation with palladium provided the trimethylsilylalkyne **10**.[8] Removal of the silyl group, hydrotitanation, and aqueous workup gave (*Z*)-silylalkene **11**, which was easily converted into the vinyl iodide **3**.[9]

The synthesis of fragment **4** started with commercially available neopentyl glycol **13**. Compound **13** was protected as



Scheme 2. a) DIBAL-H, CH_2Cl_2, $-78\,^{\circ}C$, 70%; b) $Ph_3P{=}C(Me)CHO$, benzene, reflux, 90%; c) Et_2AlCl, ligand **12**, TMSCN, $Bu_3P(O)$, CH_2Cl_2, $-40\,^{\circ}C$, 97%, 99% *ee*; d) H_2SO_4, EtOH, reflux, 75%; e) *t*$BuMe_2SiCl$, imidazole, DMF, 99%; f) DIBAL-H, toluene, $-78\,^{\circ}C$, 87%; g) $Me_3SiC{\equiv}CLi$, THF, $-78\,^{\circ}C$; then methyl chloroformate, 79%; h) $Pd(OAc)_2$, Bu_3P, HCO_2NH_4, benzene, $50\,^{\circ}C$, 51%; i) AcOH, THF, H_2O, $50\,^{\circ}C$, 89%; j) $[Ti(O\,i\mathrm{Pr})_4]$, *i*PrMgCl, Et_2O, $-78\rightarrow-50\,^{\circ}C$, 90%; k) I_2, CH_2Cl_2, 65%; l) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 90%. Bn = benzyl, DIBAL-H = diisobutylaluminum hydride, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

monobenzyl ether **14**, which was then oxidized to aldehyde **15** (Scheme 3). The lithium enolate of butanone was allowed to react with **15**, and the resulting alcohol was transformed into enone **16** by the use of trifluoroacetic anhydride and DBU. As planned a catalytic asymmetric epoxidation of **16** was extensively examined.[5] However, because of the steric hindrance of the quaternary carbon atom in the α-position to the double bond, only small amounts of the epoxide were

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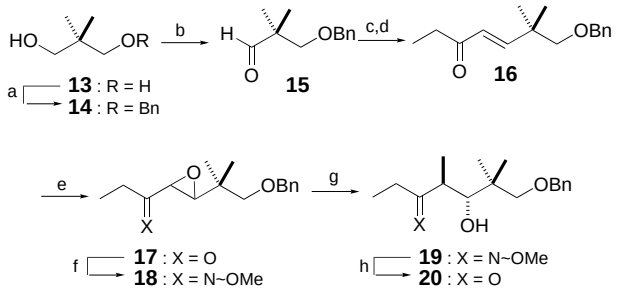


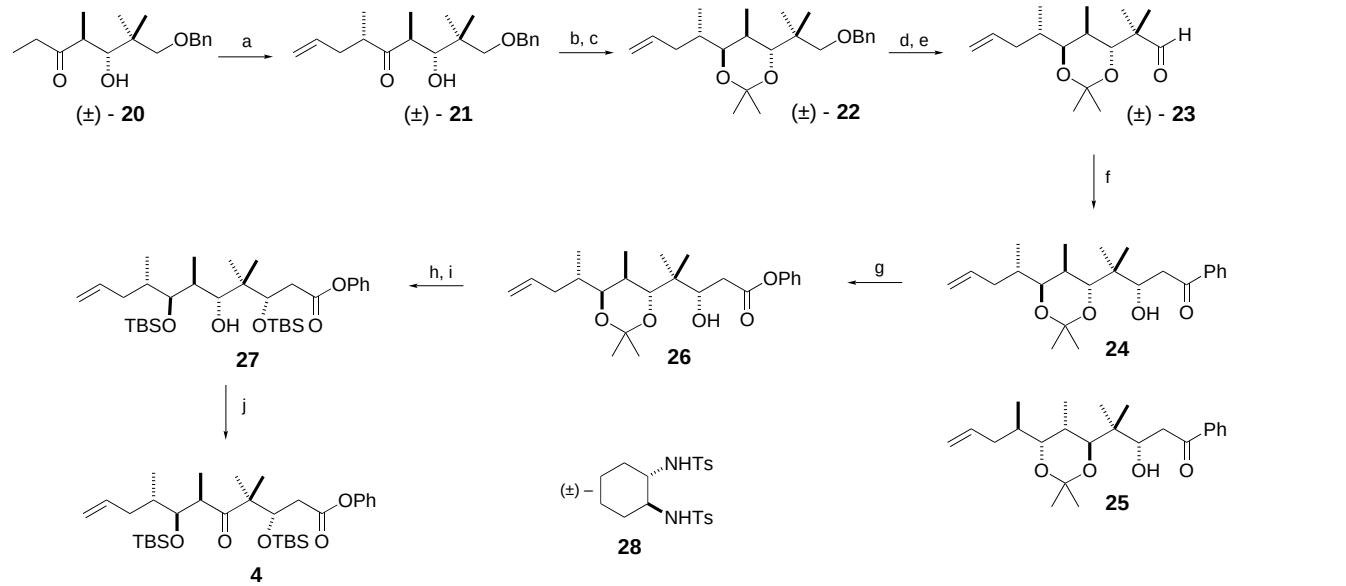
Scheme 3. a) NaH, BnBr, DMF, 72%; b) $SO_3 \cdot Py$, DMSO, Et_3N, 96%; c) LDA, butanone, THF, $-78\,^{\circ}C$, 81%; d) trifluoroacetic anhydride, CH_2Cl_2, then DBU, 100%; e) H_2O_2, NaOH (aq), MeOH, 66%; f) NH_2-OMe · HCl, AcONa, MeOH, 83%; g) CuCN, MeLi, Et_2O, $-78\,^{\circ}C$, 60%; h) Raney nickel (W2), H_2, H_3BO_3, acetone, THF, MeOH, H_2O, 78%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, LDA = lithium diisopropylamide, Py = pyridine.

obtained with low *ee* values. This unfortunate result led us to another strategy for the synthesis of optically active **4**. We envisioned that a direct aldol reaction of acetophenone with (±)-**23** (see Scheme 4) promoted by a heteropolymetallic asymmetric catalyst would give the desired **24** by an effective catalyst-controlled process. Toward this end, **16** was oxidized with H_2O_2 to the epoxy ketone **17**, which was then converted into methyloxime **18** (Scheme 3). The epoxide opening to give *anti*-aldol **20** was achieved using cuprate reagent (→**19**) and subsequent reduction with Raney nickel followed by hydrolysis.[10] To the best of our knowledge, this is a new method to prepare an *anti*-aldol.[11]

The lithium enolate of aldol **20** was treated with allyl bromide to give **21** as a single stereoisomer (Scheme 4).[12] Reduction of **21** with $Me_4NBH(OAc)_3$ provided the desired diol as the major compound (ca. 7:1), which was then protected as an acetonide (→**22**).[12] The benzyl group of **22** was cleaved under Birch reduction conditions, and the resulting alcohol was oxidized to aldehyde **23**, which was a key compound for the crucial catalytic resolution. We examined a direct catalytic asymmetric aldol reaction of acetophenone with (±)-**23** using the heteropolymetallic catalyst [$LaLi_3${tris(binaphthoxide)}] (LLB) with KOH and H_2O.[6] Gratifyingly, as expected, the resolution was achieved and the two diastereomers **24** and **25** were formed with high *ee* values in a catalyst-controlled manner using 20 mol% of catalyst (30% yield, 89% *ee* for **24**; 29% yield, 88% *ee* for **25**; recovery of **23**, 30%).[13]

Thus we succeeded in obtaining the two optically active compounds **24** and **25** simultaneously, and therefore a strategy of this type would be useful for exploring the diversity of epothilones in terms of medicinal chemistry. As far as we know, this is the first example of a catalytic resolution of the *racemic* compound in an aldol reaction using a simple asymmetric catalyst.[2k] The desired compound **24** for the synthesis of epothilone A was transformed into phenyl ester **26** using bis(trimethylsilyl) peroxide (BTSP) and $SnCl_4$; the terminal olefin remained unchanged.[14] Deprotection and selective reprotection of hydroxyl moieties gave **27**, which was immediately oxidized to **4** by Dess–Martin periodinane to avoid the undesired cyclization of hydroxy and ester moieties.

Suzuki coupling of fragments **3** and **4** and subsequent hydrolysis under basic conditions afforded the hydroxy acid **29** (Scheme 5).[2a] Ring closure of **29** under Yamaguchi conditions afforded cyclic compound **30**.[2d,g,i–k] Finally removal of the two TBS groups and epoxidation of the ring olefin functionality afforded **1**.[2a,c,i,j]



Scheme 4. a) LHMDS, allyl bromide, DMPU, THF, $-78\,^{\circ}C$, 48% (recovery of **20** 52%); b) $Me_4NBH(OAc)_3$, AcOH, MeCN, 74%; c) methoxypropene, TsOH, DMF, 96%; d) Li, liq. NH_3, *t*BuOH, THF, 100%; e) TPAP, NMO, 4-Å molecular sieves, CH_2Cl_2, 89%; f) acetophenone, (*R*)-LLB, KHMDS, H_2O, THF, $-20\,^{\circ}C$, 30% (89% *ee*) for **24**, 29% (88% *ee*) for **25** (recovery of **23** 36%); g) BTSP, $SnCl_4$, 4-Å molecular sieves, ligand **28**, K_2CO_3, CH_2Cl_2, 71%; h) BCl_3, CH_2Cl_2, $-78\,^{\circ}C$, 77%; i) TBSOTf, iPr_2NEt, CH_2Cl_2, 100%; j) Dess–Martin periodinane, CH_2Cl_2, 65%. BTSP = bis(trimethylsilyl) peroxide, DMPU = 1,3-dimethylhexahydro-2-pyrimidinone, KHMDS = potassium bis(trimethylsilyl)amide, LHMDS = lithium bis(trimethylsilyl)amide, LLB = [$LaLi_3${tris(binaphthoxide)}], NMO = 4-methylmorpholine *N*-oxide, OTf = trifluoromethanesulfonate, TPAP = tetrapropylammonium perruthenate, Ts = toluene-4-sulfonyl.

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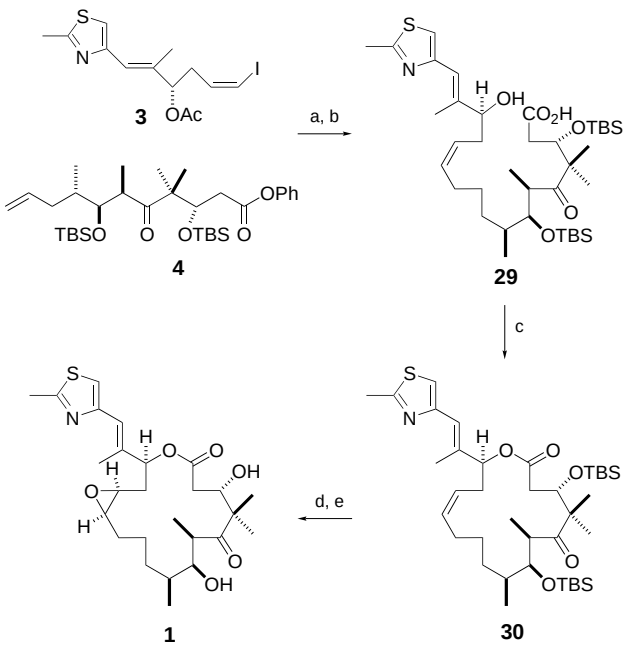

Scheme 5. a) 9-BBN (2 mol equiv), THF, then $[PdCl_2(dppf)]$ (50 mol %), K_3PO_4, DMF, H_2O, 60 °C, 50 %; b) NaOH (aq), MeOH, 84 %; c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene, 88 %; d) HF·pyridine, THF, 99 %; e) 3,3-dimethyldioxirane, CH_2Cl_2, −35 °C, 49 %. 9-BBN = 9-borabicyclo[3.3.1]nonane, DMAP = 4-dimethylaminopyridine, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

In summary we have succeeded in an enantioselective total synthesis of epothilone A (**1**) using multifunctional asymmetric catalyses with a direct aldol reaction and cyanosilylation as key steps.

Experimental Section

24, **25**: To a stirred solution of KHMDS in toluene (532 μL, 0.266 mmol, 0.5 M) at 0 °C was added a solution of water in THF (590 μL, 0.59 mmol, 1.0 M). The resulting solution was stirred for 20 min at 0 °C, and then (*R*)-LLB in THF (2.95 mL, 0.295 mmol, 0.1 M) was added and the mixture was stirred at 0 °C for 30 min. The pale yellow solution thus obtained was then cooled to −20 °C, and acetophenone (1.38 mL, 11.8 mmol) was added. The solution was stirred for 20 min at this temperature and then **23** (397 mg, 1.48 mmol) was added and the reaction mixture was stirred for 168 h at −20 °C. The reaction was quenched by addition of 1 N HCl (4 mL), and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (SiO_2, ethyl acetate/hexane 1/30) to give **24** (172 mg, 30 %, 89 % *ee*) and **25** (166 mg, 29 %, 88 % *ee*).

7: Ligand **12** (447 mg, 0.625 mmol) was placed in a flame-dried flask and dried at 50 °C for 2 h under reduced pressure. Dichloromethane (2 mL) was added, followed by the addition of diethylaluminum chloride in hexane (651 μL, 0.625 mmol, 0.96 M) under argon atmosphere. After the mixture was stirred for 10 min, tributylphosphane oxide (546 mg, 2.5 mmol) in dichloromethane (1.8 mL) was added at room temperature. The resulting mixture was stirred at the same temperature for 1 h to give a clear solution. To this stirred solution of the catalyst was added **6** (1.045 g, 6.25 mmol) in dichloromethane (13.8 mL) at −40 °C. After 30 min TMSCN (1.0 mL, 7.5 mmol) was slowly added over 24 h with a syringe pump. (Because the melting point of TMSCN is 11–12 °C, it should be added dropwise from the top of the flask, where the temperature may be above 15 °C.) The reaction mixture was stirred for 39 h at the same temperature. Trifluoroacetic acid (2.0 mL) was added at −40 °C, and the mixture was stirred vigorously at room temperature for 1 h to hydrolyze the trimethylsilyl ether moiety of the product. After the addition of ethyl acetate (30 mL), the mixture was stirred for further 30 min. The organic layer was separated and washed with water. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude product was further purified by flash chromatography (ethyl acetate/hexane 1/3) to give **7** (1.18 g, 97 %, 99 % *ee*).

General procedure for the epoxide opening reaction using a cuprate reagent (see Table 1, entry 1):[11] To a suspension of CuCN in diethyl ether was added methyllithium in diethyl ether (4.9 mL, 5.36 mmol, 1.1 M) at −78 °C. Then the temperature was gradually raised to 0 °C, and the mixture was stirred for 20 min to give a clear solution. To the solution was added the epoxy-oxime (99.3 mg, 0.54 mmol) in diethyl ether (2.0 mL), and the resulting mixture was stirred for 24 h at the same temperature. Then saturated aqueous NH_4Cl and aqueous NH_3 were added, and the mixture was stirred at room temperature for 1 h. The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude product was further purified by flash chromatography (ethyl acetate/hexane 1/20) to give the methyloxime alcohol (83 mg, 77 %).

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1871 – 1873; b) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168 – 4178.

[7] The absolute configuration was determined by Mosher's method; see J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512 – 519. The enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALPAK AD (2-propanol/hexane 1/100).

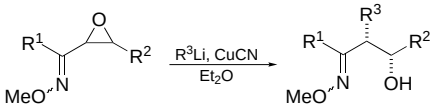
[8] a) T. Mandai, T. Matsumoto, M. Kawada, J. Tsuji, *Tetrahedron Lett.* **1993**, *34*, 2161 – 2164; b) J. Tsuji, T. Sugiura, I. Minami, *Synthesis* **1987**, 603 – 606.

[9] a) K. Harada, H. Urabe, F. Sato, *Tetrahedron Lett.* **1995**, *36*, 3203 – 3206; b) F. Sato, H. Ishikawa, M. Sato, *Tetrahedron Lett.* **1981**, *22*, 85 – 88. This method could lead to the fragment for the synthesis of epothilone B (**2**).

[10] For related work with oximes, see E. J. Corey, L. S. Melvin, Jr., M. F. Haslanger, *Tetrahedron Lett.* **1975**, 3117 – 3120.

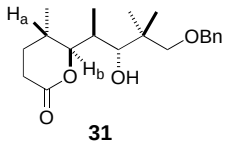
[11] We can also prepare *syn*-aldol from *cis*-enone by this method.[13] Through coupling with the stereocontrolled catalytic asymmetric epoxidation of the *cis*- and *trans*-enones recently developed in our group,[5] it is possible to prepare *syn*- and *anti*-aldol from *cis*- and *trans*-enones, respectively, with excellent *ee* values (Table 1).

Table 1. Epoxide opening of *cis*-epoxy-oximes by cuprate reagents.



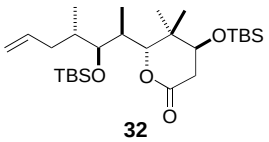
Entry	R^1	R^2	R^3	Yield [%]
1	methyl	pentyl	methyl	77
2	propyl	pentyl	methyl	72
3	phenethyl	pentyl	methyl	85
4	phenethyl	pentyl	butyl	80
5	phenethyl	pentyl	phenyl	80
6	phenethyl	pentyl	vinyl	50
7	pentyl	phenethyl	methyl	81

[12] The relative configuration of the alcohol resulting from reduction of **21** with $Me_4NBH(OAc)_3$ was determined by analyzing the NOE of **22**, and the relative configuration of the methyl group of **22** resulting from allylation of **20** was further determined by transforming **22** into **31** and analyzing the coupling constant between H_a and H_b (10.2 Hz).

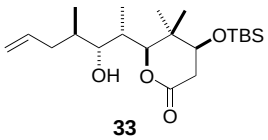


31

[13] The absolute configurations were determined by Mosher's method,[8] and the enantiomeric excesses were determined by HPLC analysis using DAICEL CHIRALPAK AD (2-propanol/hexane 1/100). The relative configurations were determined by transforming **24** into **32** and **25** into **33** (cyclization of **27** and **34**, respectively), and analyzing their NOEs.



32



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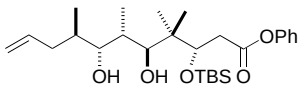

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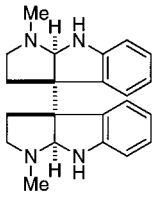
[14] R. Göttlich, K. Yamakoshi, H. Sasai, M. Shibasaki, *Synlett* **1997**, 971 – 973.

Enantioselective Construction of Vicinal Stereogenic Quaternary Centers by Dialkylation: Practical Total Syntheses of (+)- and *meso*-Chimonanthine**

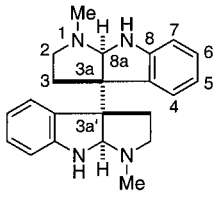
Larry E. Overman,* Jay F. Larrow, Brian A. Stearns, and Jennifer M. Vance

Enantioselective formation of vicinal stereogenic quaternary carbon centers is one of the more formidable challenges in contemporary organic synthesis.[1, 2] Here we report a powerful method for creating such arrays by reaction of achiral dienolates with a chiral, enantiopure dielectrophile. The method was developed to address the vicinal stereogenic quaternary benzylic carbon centers that are the signature structural feature of indole alkaloids containing the hexacyclic 3a,3a′-bispyrrolidino[2,3-*b*]indoline unit.

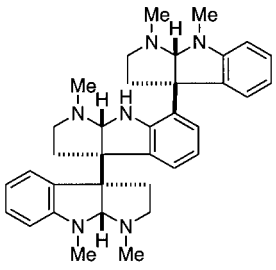
The chimonanthines are the simplest members of this family and are found in nature in all three stereochemical motifs: *meso*-chimonanthine (**1**)[3] and (−)-chimonanthine[4] from plant sources; (+)-chimonanthine (**2**) from the skin of a Colombian frog[5] and from plant sources.[6] In addition, many



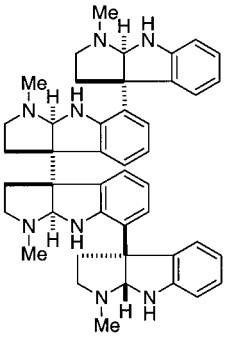
1: *meso*-chimonanthine



2: (+)-chimonanthine



3: (–)-idiospermuline



4: quadrigemine C

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

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