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Asymmetric Total Synthesis of (−)-Indicol by a Carbene Cyclization–Cycloaddition Cascade Strategy

Sze Kui Lam and Pauline Chiu*[a]

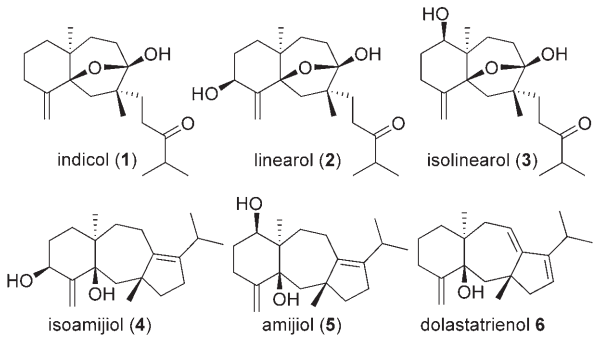
Abstract: The first total synthesis of a secodolastane, (−)-indicol, has been accomplished. The key reaction is a rhodium(II)-mediated carbene cyclization–cycloaddition cascade, by which the core bicyclo[5.4.0]undecane skeleton was assembled. In this one-pot reaction, a domino series of transformations resulting in the construction of three σ bonds and three stereocenters was realized in good yield.

Keywords: cascade reactions · indicol · rhodium · total synthesis

Introduction

The carbene cyclization–cycloaddition cascade (CCCC) reaction is a powerful domino process that can construct complex polycyclic structures efficiently.[1] In this one-step reaction catalyzed by metal complexes, three distinct σ bonds are forged, resulting in the creation of up to four new stereocenters. By today's standards in which synthetic efficiency and atom economy is as important as successfully synthesizing the targets themselves, the CCCC reaction represents a useful synthetic methodology to access systems bearing multiple rings. The utility of this reaction in the construction of complex molecular architectures has been clearly demonstrated by its application in the formal and total syntheses of complex natural products, including (±)-aspidophytine,[2] (±)-illudin M,[3] (±)-vallesamidine,[4] (±)-lycopodine,[5] (±)-epoxysorbicillinol,[6] (±)-nemorensic acid,[7] (+)-zaragozic acids A[8] and C,[9] (−)-polygalolides A and B,[10] (−)-colchicine,[11] and (−)-pseudolaric acid A.[12] The application of this cascade reaction in total synthesis has already led to a greater understanding of its scope and has led to further development of this reaction as a tool for synthesis.[13]

Indicol (**1**) is a secodolastane diterpenoid isolated from the brown alga, *Dictyota indica*, from the Arabian Sea.[14] Ahmad et al. reported that the extraction of one kilogram of dried *Dictyota indica* yielded 15 mg of indicol (**1**) plus minute amounts of other secodolastanes, including linearol (**2**) and isolinearol (**3**). Linearol[15] and isolinearol[16] had also been previously isolated from the related *Dictyota cervicornis* and *Dictyota linearis*, respectively. Secodolastanes have recently been demonstrated to have antifeedant effects on herbivores. Experiments showed that when ulva was spiked with secodolastanes, its consumption by the marine gastropod, *Astraea latispina*, was significantly inhibited.[17]



The secodolastanes have characteristic bicyclo[5.4.0]undecane carbon frameworks, which is further constricted through a transannular cyclization by a tertiary alcohol to form a hemiacetal functionality, so that the carbobicyclic skeleton is not an extended platform but is folded back as a more compact scaffold. Each secodolastane has a cyclohexane ring A bearing an exocyclic methylene group, fused with a cycloheptane ring B, the latter being geminally substituted by an ethylene isopropyl ketone moiety and a methyl group. The members of the secodolastane family are various

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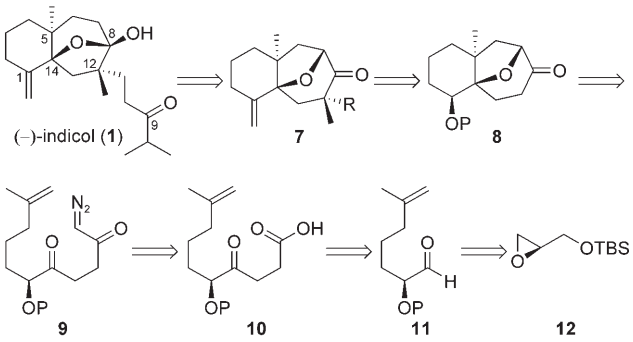
oxygenated derivatives of this basic carboskeleton, and indicol appears to be the simplest member of this family yet discovered, although it nonetheless harbors in its congested core two pairs of vicinal stereocenters, of which two are quaternary.

The absolute configuration of indicol is assumed to be the same as that of linearol, the structure of which was deduced from chemical correlation with its biogenetic dolastane precursor of known absolute stereochemistry, isoamijiol (**4**).[18] Amijiol (**5**), the precursor of isolinearol, has also been isolated, whereas the corresponding parent dolastane of indicol has not yet been reported.[18] The dolastanes are tricyclic natural products isolated from the same algal species, and are characterized by the presence of an additional cyclopentane ring C fused to the AB rings of the secodolastanes. The dolastanes have been reported to show a wide range of biological activities, including cytotoxicity, histamine antagonism, antifungal, and antibiotic effects.[18–21] Interestingly, they are structural relatives of the potent antibiotic, guanacastepene A.[22]

Several dolastanes, such as isoamijiol (**4**), dolastatrienol **6**, and 14-deoxyisoamijiol, have been successfully synthesized as racemates and as the unnatural antipodes.[23–27] Coincidentally, all but one of these total syntheses are based on appending ring A last,[27] that is, a BC→ABC strategy, probably due to the ubiquity of perhydroazulene systems in natural products, and the myriad of methodologies available to gain access to the final six-membered ring. While the syntheses of the more adorned dolastanes have been reported, the total synthesis of any secodolastane has yet to appear in the literature, although there have been synthetic studies.[28] Insofar as the secodolastanes are the likely metabolites of the dolastanes in nature, a direct chemoselective oxidative conversion of a dolastane into a secodolastane in the laboratory is not straightforward due to the presence of competing olefin functionalities that necessitates additional protection and manipulations.

The successful total synthesis of indicol would provide an independent confirmation of its absolute configuration, which would have stereochemical implications for the other members of the secodolastane family as well. Furthermore, the route toward indicol would serve as a basis for the synthesis of the more complex secodolastanes, as well as a novel entry into the dolastane skeleton by an unexplored AB→ABC strategy. Moreover, the bioactivity profile of indicol has not been reported. All these considerations motivated us to synthesize this natural product in an enantioselective and stereocontrolled manner. To us, the oxatricyclic structure of indicol seems to be ideally suited for showcasing the assembly of polycyclic frameworks by using the carbene cyclization–cycloaddition cascade reaction.[29,30]

Synthetic plan: Our retrosynthetic analysis of indicol (**1**) based on the CCCC strategy is outlined in Scheme 1. We envisioned that the hemiacetal functionality in **1** could be derived from the reductive ring opening of oxygen-bridged ketone **7**. The required bis-α-substitution and methylenation



Scheme 1. Retrosynthetic analysis of indicol.

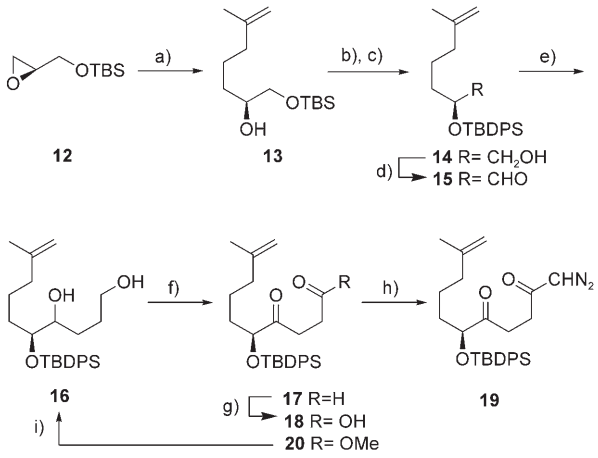
in **7** should be accessible from ketone **8**. The key oxatricyclic framework in **8** is a CCCC cycloadduct obtained from the reaction of chiral α-diazoketone **9**, in which the stereochemically defined protected hydroxyl substituent could confer stereoselectivity in this domino reaction, as our previous studies indicated.[12] The precursor of **9** is carboxylic acid **10**, which in turn could be obtained from the homologation of aldehyde **11.** There are various strategies to acquire this chiral intermediate, and we elected to use the commercially available TBS-protected glycidol **12** as the starting material.

Results and Discussion

Synthesis of the diazoketone for CCCC reaction: The commercially available chiral oxirane (*S*)-**12** was ring-opened at the less-hindered site in high yield by 3-methylbut-3-enyl magnesium bromide in the presence of copper(I) cyanide. This provided alcohol **13** bearing the stereochemical element that would direct the entire synthesis. This key hydroxyl stereocenter was secured by protection using TBDPSCl. The elaboration of the other terminus was initiated by deprotection of the TBS group to reveal alcohol **14**, followed by oxidation under Swern conditions to yield aldehyde **15**. Treatment of **15** by using Normant's Grignard reagent[31] provided the desired diol **16** exclusively in high yield, without any interfering silyl group migrations.

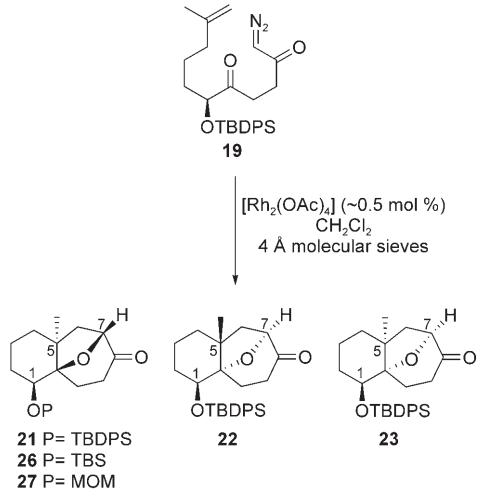
To avoid the formation of intermediary lactol or lactone species that would result in the premature arrest of the desired bisoxidation, a second Swern oxidation was employed to convert diol **16** to γ-ketoaldehyde **17** exclusively. Subsequently, a Lindgren oxidation[32] smoothly converted the ketoaldehyde **17** to ketoacid **18**. Activation of the acid by isobutyl chloroformate[33] and treatment with excess diazomethane afforded α-diazoketone **19**, accompanied by some methyl ester **20** which could be recycled for use by reduction (Scheme 2).

CCCC reaction of diazoketone 19: With α-diazoketone **19** in hand, we proceeded to examine the pivotal Rh^{II}-mediated CCCC reaction to construct the carbocyclic platform of indicol. When **19** was treated with a catalytic amount of rhodium(II) catalyst, the anticipated CCCC reaction proceeded



Scheme 2. a) $CH_3(C{=}CH_2)CH_2CH_2MgBr$, CuCN, THF, 4 h, −78 °C, 93 %; b) TBDPSCl, imidazole, DMF, overnight, RT; c) PPTS, MeOH, 4 d, RT, 84 % for 2 steps; d) DMSO, $(COCl)_2$, CH_2Cl_2; $i$$Pr_2NEt$, 10 min, −78 °C, 93 %; e) $ClMgCH_2CH_2CH_2OMgCl$, THF, 2 h, −78 °C, 91 %; f) DMSO, $(COCl)_2$, CH_2Cl_2; $i$$Pr_2NEt$, 10 min, −78 °C, 90 %; g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, tBuOH, H_2O, RT, 88 %; h) iBuOCOCl, NEt_3, THF, Et_2O, 2 h, RT; CH_2N_2, Et_2O, 6 h, 0 °C 66 % **19** and 20 % **20**; i) 1 M DIBAL-H, CH_2Cl_2, −40 °C to RT, 4 h, 70 %. TBDPSCl = *tert*-butyldimethylsilyl chloride; PPTS = pyridinium *p*-toluenesulfonate; DIBAL-H = diisobutylaluminium hydride.

to give as products a major cycloadduct **21** and a minor diastereomeric cycloadduct **22**, generally in a ratio of about 3:1 (Scheme 3).



Scheme 3. Diastereomeric cycloadducts from the CCCC reaction of **19**.

The major diastereomer **21** is the cycloadduct containing the desired stereochemistry at the fused rings, and its structure was deduced by 2D NOE NMR spectroscopic analysis (Scheme 3). The bridgehead methyl group at C5 showed a strong NOE with the proton at C1, revealing that they are on the same face of cyclohexane ring. No NOE correlations were observed between the bridgehead methyl group with the TBDPS group or with the proton at C7. The structure of **21** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1). Thus in one step, the advanced intermediate **21** containing the nucleus of indicol and essentially

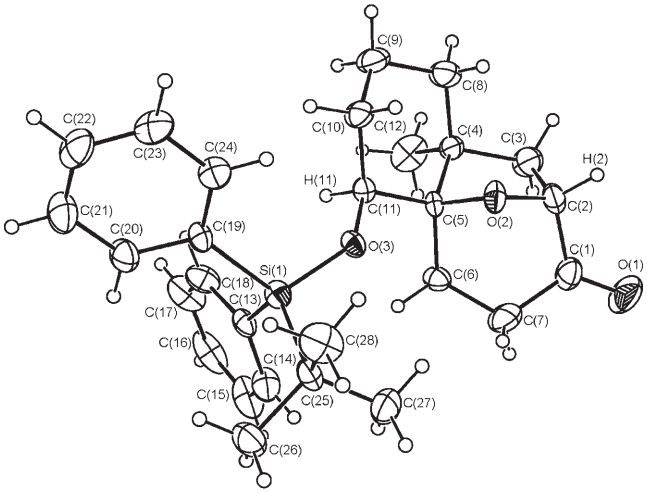
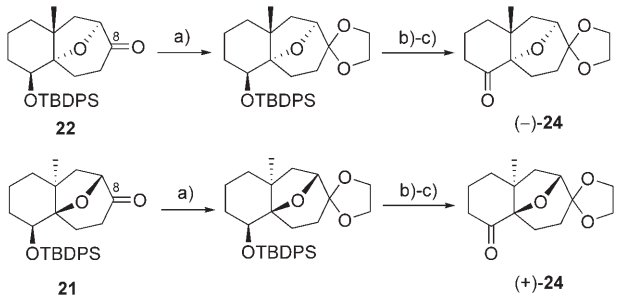


Figure 1. ORTEP of cycloadduct (±)-**21**.

three out of the four stereocenters in the target molecule was obtained through the CCCC reaction of acyclic **19**.

The minor diastereomer **22** also obtained in the CCCC reaction was deduced by 2D NMR spectroscopic analysis to have the stereochemical structure as shown (Scheme 3). Nuclear Overhauser effects were observed between the bridgehead methyl group at C5 and the phenyl groups of the TBDPS group, but no correlations were found with protons at C1 or C7. The structure of **22** was additionally confirmed by a three-step chemical conversion to ketone (−)-**24**, which showed an equal and opposite rotation compared to (+)-**24** obtained through the same series of reactions starting from **21** (Scheme 4). Incidentally, the unnatural antipode of indicol could be obtained via **22**, starting from the same chiral precursor, (*S*)-**12**.

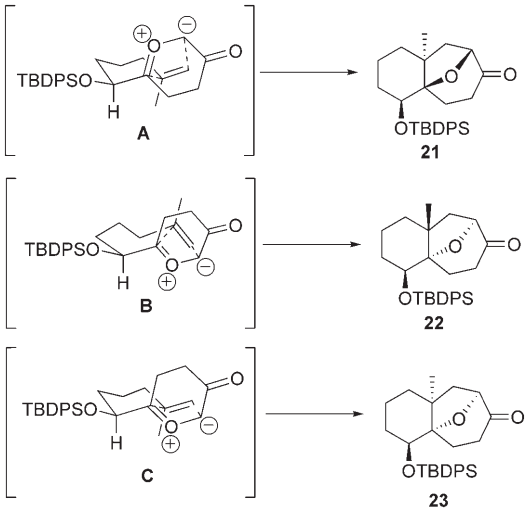
When we analyzed very carefully the product mixture from the CCCC reaction, we isolated and characterized a



Scheme 4. For **22**: a) $TMSCH_2CH_2OTMS$, TMSOTf, CH_2Cl_2, overnight, RT, 93 %; b) 1 M TBAF, THF, 40 h, reflux; c) DMSO, $(COCl)_2$, CH_2Cl_2; NEt_3, 10 min, −78 °C, 82 % for 2 steps. For **21:** a) $TMSOCH_2CH_2OTMS$, TMSOTf, CH_2Cl_2, overnight, RT; b) 1 M TBAF, 64 h, RT, 99 % over 2 steps; c) DMSO, $(COCl)_2$, CH_2Cl_2; NEt_3, 10 min, −78 °C, 98 %. TMS = trimethylsilyl; OTf = triflate; TBAF = tetrabutylammonium fluoride.

trace amount of a third diastereomeric cycloadduct **23**, produced in <5% yield. Analysis by 2D NMR spectroscopy showed NOE correlations between the methyl group at C5 with both the protons at C1 and at C7. However, for the bridgehead substituent to be proximate to the protons at C1 and C7, this is possible only if cycloadduct **23** has the structure as shown (Scheme 3). We were rather surprised to isolate this diastereomer which has the oxygen bridge and the bridgehead methyl group *syn* to each other, thus necessitating the tetrahydrofuran to be *trans*-fused with respect to ring A. This is an adduct which has never been documented before as a product of the CCCC reaction, and tends to decompose on standing for prolonged periods.

The diastereomeric cycloadducts are rationalized to be formed through transition states as shown in Scheme 5.[34]

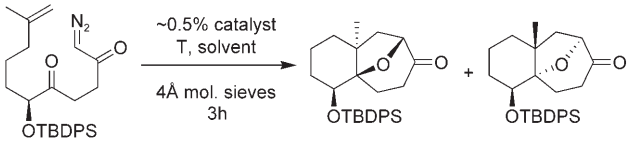


Scheme 5. Proposed transition states of the cycloaddition of the carbonyl ylide.

The major cycloadduct **21** is generated from transition-state **A** in which the tether adopts a chair conformation, with the bulky siloxy group residing in an equatorial position. The minor diastereomer **22** is formed from transition state **B** the tether of which is in a less-stable boat conformation. The least stable diastereomer **23** may be derived from transition-state C, which is destabilized due to the impending formation of a *trans*-fused five-membered ring ether.

After screening a number of reaction parameters in the CCCC reaction of **19** (Table 1), the use of dichloromethane as the solvent was found to promote the highest yields. Although the less-polar solvents hexane and trifluorotoluene appeared to give a slightly higher ratio of the desired diastereomer, this less than compensates for the corresponding decrease in the overall yield of the cycloadducts. Dirhodium(II) octanoate was found to be the best catalyst. Thus at 0°C, the CCCC reaction of **19** proceeded in 81% yield in anhydrous dichloromethane to **21** and **22** in 61 and 20% yields, respectively (Table 1, entry 2). Further decreasing the temperature did not lead to any improvement in the diastereoselectivity. Importantly, (−)-**21** thus prepared was found to have 99% *ee* by chiral HPLC analysis, compared with (±)-**21** prepared by the same route starting from (±)-**12**. This verified that racemization did not occur in the course of the reactions.

Table 1. CCCC reaction mediated by achiral Rh^{II} catalysts.

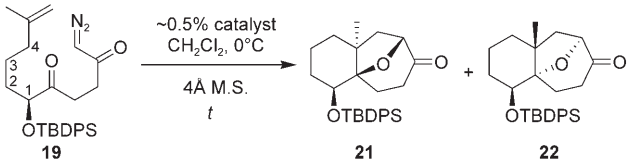


Entry	Catalyst[a]	Solvent	T [°C]	Yield (**21**+**22**) [%]	dr (**21**:**22**)
1	$[Rh_2(Oct)_4]$	CH_2Cl_2	RT	77	2.7:1
2	$[Rh_2(Oct)_4]$	CH_2Cl_2	0	81	3.1:1
3	$[Rh_2(Oct)_4]$	CH_2Cl_2	−15	74	3.1:1
4	$[Rh_2(Oct)_4]$	hexane	0	60	3.6:1
5	$[Rh_2(Oct)_4]$	CF_3Ph	0	50	3.5:1
6	$[Rh_2(OAc)_4]$	CH_2Cl_2	RT	64	3.3:1
7	$[Rh_2(OAc)_4]$	CH_2Cl_2	0	65	3.1:1
8	$[Rh_2(OAc)_4]$	CH_2Cl_2	−15	65	2.3:1
9	$[Rh_2(OAc)_4]$	hexane	0	<15	n.d.[b]
10	$[Rh_2(OAc)_4]$	CF_3Ph	0	<15	n.d.
11	$[Rh_2(OCOCF_3)_4]$	CH_2Cl_2	0	<15	n.d.

[a] Oct = octanoate. [b] n.d. = not determined.

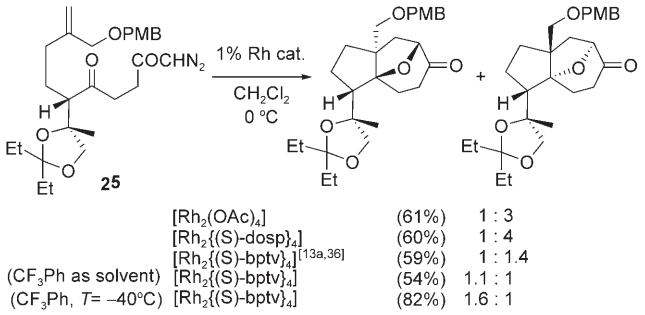
In an effort to improve the diastereoselectivity of the CCCC reaction, chiral rhodium(II) catalysts were screened in the reaction of chiral diazoketone **19** to evaluate the extent of reagent control (Table 2). However, for the catalysts that were tried, only a limited or negligible change in the ratio of **21**/**22** was observed. In our previous studies, the CCCC reaction of cycloaddition substrates, such as **25**, which has a three-carbon tether, had been more responsive to the effect of solvent, temperature, and chiral catalysts,[12] for example, the diastereoselectivity could change 5–6-fold on varying the rhodium catalysts (Scheme 6). We surmise

Table 2. CCCC reaction mediated by chiral Rh^{II} catalysts.

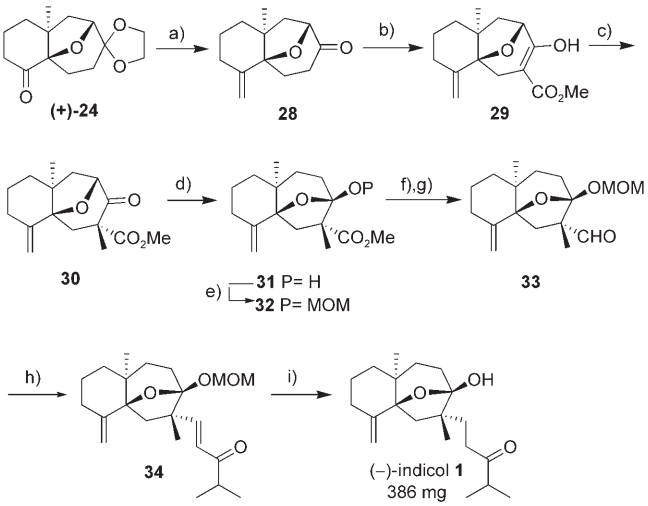


Entry	Catalyst[a]	t [h]	Yield (**21**+**22**) [%]	dr (**21**:**22**)
1	$[Rh_2\{(R)\text{-dosp}\}_4]$	3	82	2.3:1
2	$[Rh_2\{(S)\text{-dosp}\}_4]$	3	58	2.9:1
3	$[Rh_2\{(S)\text{-ntpa}\}_4]$	48	78	3.1:1
4	$[Rh_2\{(S)\text{-nttl}\}_4]$	3	68	3.5:1
5	$[Rh_2\{(S)\text{-npv}\}_4]$	3	68	3.3:1
6	$[Rh_2\{(S)\text{-bptv}\}_4]$	3	52	2.7:1

[a] For catalysts see ref. [36]. dosp = (*N*-dodecylbenzenesulfonyl)prolinate; ntpa = 1,8-naphthdioyl phenylalaninate; nttl = 1,8-naphthdioyl *tert*-leucinate; npv = 1,8-naphthdioyl valinate; bptv = *N*-benzene-fused phthaloyl valinate.



Scheme 6. CCCC reaction of **25** containing a three-carbon tether.



Scheme 7. a) Ph_3PCH_3Br, 1.6 M *n*BuLi, THF, 2 h, RT, then, 3 M HCl, overnight, reflux, 95%; b) LDA, THF, 1 h, −78 °C; $NCCO_2Me$, 2 h, −78 °C, 0.005 M, 88%; c) NaH, THF, 1 h, RT; MeI, 2 h, RT, 0.005 M, 81%; d) SmI_2, MeOH, THF, 1 h, 0 °C, 0.002 M, 91%; e) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 156 h, RT, 92%; f) LAH, Et_2O, 4 h, RT; g) DMSO, $(COCl)_2$, CH_2Cl_2; Et_3N, 10 min, −78 °C; h) NaH, dimethyl(3-methyl-2-oxobutyl)-phosphonate, THF, overnight, RT, 90% over 3 steps from **36**; i) $[Ph_3P(CuH)]_6$, THF, H_2O, 24 h, RT; then 12 M HCl, MeOH, 48 h, RT, 98%. MOM = methoxymethyl.

that because the cycloaddition of **19**, which has a four-carbon (C1 to C4) tether between the dienophile and the carbonyl ylide, was slower,[35] the rhodium catalyst may have only a weak association with, or may have even dissociated fully from the carbonyl ylide during the cycloaddition event. Thus the chirality of the catalysts did not exert a great influence on the cycloaddition; as a consequence, the diastereomeric ratio between cycloadducts **21** and **22** in the CCCC reaction with chiral or achiral catalysts remained at about 3:1 (Table 2).

Total synthesis of indicol (1): To complete the total synthesis of indicol, further functionalizations of **21** including the installation of the two substituents α to the carbonyl group, olefination at C1, and the formation of hemiacetal remain to be accomplished.

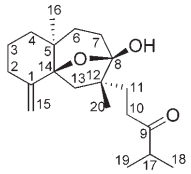
The direct alkylation of the enolate of **21** with various alkyl halides was attempted under many reaction conditions, but the use of various bases, as well as variation of temperature, solvents, and additives failed to produce the desired monoalkylated product. Even when **21** was converted to the less sterically demanding TBS-protected **26** or MOM-protected **27** (Scheme 3), the alkylation of these ketones still met with failure. Both the ketones and the alkyl halides could largely be recovered.

Thus the transformations were resequenced to first convert the protected hydroxyl group at C1 to the less sterically demanding exocyclic methylene group. To this end, it was necessary to temporarily protect the ketone at C8 to avoid competitive reaction at a later stage. After **21** was protected as the ketal, desilylation and oxidation afforded ketone (+)-**24** (Scheme 4). Treatment of **24** under typical Wittig conditions, followed by a relatively vigorous acid workup, induced both methylenation and deketalization in the same pot to furnish ketone **28** in high yield (Scheme 7). No isomerization of the exocyclic olefin was observed.

Even though **28** is less hindered than **21**, alkylation of **28** via its enolate remained disappointingly problematic and afforded low yields of alkylation product. Ultimately, α-dialkylation was indirectly accomplished by the intermediacy of ketoester **29** (Scheme 7). Reaction of **28** with Mander's reagent under dilute conditions (≈0.005 M) led to an 88% yield of ketoester **29**, which was predominantly in the enol form. At typical reaction concentrations (≈0.3 M), however, the methoxycarbonylation of **28** proceeded to give **29** with diminished yields of ≈60%. Subsequently, methylation of **29** proceeded readily with predictably high *syn* selectivity with respect to the oxygen bridge, to install the final quaternary stereocenter at C12, affording β-ketoester **30** as a single diastereomer.

Reductive cleavage of ketoester **30** proceeded by treatment with freshly prepared SmI_2 in THF at 0 °C to give a hydroxyketone that spontaneously underwent transannular cyclization to hemiacetal **31** (Scheme 7). In this reaction, a dilute reaction concentration (≈0.002 M) ensured a reproducibly clean reaction and high yield of product. At this stage, we found it beneficial to protect **31**. Even though this increased the overall number of steps in the synthetic route, the subsequent transformations occurred in near quantitative yields and were found to be much cleaner than by directly using hemiacetal **31** as substrate. Protection by MOMCl required a rather long time for complete reaction, attesting to the hindrance of the structure of **31**. Mixed acetal **32** thus obtained was subjected to reduction, then oxidation to afford aldehyde **33** (Scheme 7). Then **33** underwent a smooth Horner–Emmons reaction to afford enone **34**. The yield over these three steps was 90%. Finally enone **34** was chemoselectively reduced by a Stryker reduction,[37] and after an acidic workup that also accomplished the deprotection of the MOM in the same pot, 386 mg of (−)-indicol (**1**) was furnished in excellent yield. The spectral data (Table 3) and optical rotation of synthetic (−)-indicol (**1**) thus obtained were in full accordance with literature values in all respects,[14] and confirms by chemical synthesis the pre-

Table 3. Comparison of the ^{13}C NMR ($CDCl_3$) data reported for (−)-indicol (**1**) and that reported in this work.



Number	lit.[14] δ [ppm] (75 MHz)	Exptl δ [ppm] (125 MHz)
C1	148.7	148.5
C2	34.4	34.4
C3	32.7	32.6
C4	23.3	23.2
C5	37.0	37.0
C6	32.6	32.5
C7	30.0	29.9
C8	104.8	104.7
C9	215.0	214.8
C10	28.7	28.6
C11	36.2	36.2
C12	44.1	44.1
C13	40.7	40.7
C14	84.1	84.0
C15	108.4	108.2
C16	21.5	21.5
C17	41.0	40.9
C18[a]	18.35	18.3
C19[a]	18.38	18.4
C20	23.0	22.9

[a] Assignments may be reversed.

viously proposed absolute stereochemistry of natural indicol.

Conclusion

The asymmetric total synthesis of (−)-indicol (**1**) has been successfully accomplished through a 21-step reaction sequence by starting from an optically-active, commercially-available glycidol derivative. The CCCC reaction was the key strategy for efficiently accessing the bicyclo-[5.4.0]undecane skeleton and setting up the stereocenters at C5, and C14, and essentially at C8 as well. Moreover, the bicyclic adduct in this CCCC reaction provided the required functional groups and the facial bias to enable the stereoselective dialkylation to create the final stereocenter at C12. The reactions in this route have been optimized to furnish **1** in an overall yield of 10.2% starting from the commercially available oxirane (*S*)-**12**. This first total synthesis of (−)-indicol provides a basis for the preparation of other secodolastanes, as well as a novel entry into the dolastanes. Research in these directions is in progress.

Experimental Section

General methods: All anhydrous reactions were performed in oven-dried glassware under a positive pressure of dry argon. All reaction solvents were dried and distilled. Flash chromatography was performed with E. Merck silica gel 60 (230–400 mesh ASTM). Components were visualized by illumination with a short-wavelength UV-light and/or staining. Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance spectra were obtained in $CDCl_3$ unless otherwise indicated, with tetramethylsilane as internal standard at ambient temperature on Bruker DPX 300 and 500, Bruker Avance 400, and 600 spectrometers. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and, br, broad. IR absorption spectra were recorded on a Bio-Rad FTS 165 spectrometer as a solution in CH_2Cl_2 from 4000 to 400 cm^{-1}, with subtraction for solvent. Mass spectra (MS) were recorded on a Finnigan MAT 95 mass spectrometer at both low and high resolutions, with accurate mass reported for the molecular ion (M^+) or the next largest fragment ion thereof. Optical rotations were recorded on a Perkin–Elmer 343 Polarimeter.

Compound 13: Magnesium (3.79 g, 156.31 mmol) was added to a solution of 1,2-dibromethane (0.10 mL, 1.16 mmol) in THF (50 mL) at room temperature. The mixture was heated to reflux for 5 min. 4-Bromo-2-methyl-1-butene (15.89 g, 106.63 mmol) in THF (350 mL) was added by cannula. The mixture was heated to reflux for 1 h. The Grignard reagent was transferred by cannula to a round-bottomed flask containing CuCN (0.59 g, 6.70 mmol) at room temperature. The mixture was cooled to −78 °C. Epoxide (−)-**12** (10.72 g, 57.56 mmol) in THF (100 mL) was added slowly. The resulting mixture was stirred for 4 h at −78 °C. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 5–8% EtOAc in hexane to afford alcohol **13** (13.80 g, 93%) as a colorless oil. R_f: 0.50 (10% EtOAc in hexane); $[\alpha]_D^{20} = +3.38$ (c = 2.90 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.62$ (s, 1H), 4.60 (s, 1H), 3.58–3.52 (m, 2H), 3.35 (dd, $J = 9.6$, 7.1 Hz, 1H), 2.54 (d, $J = 2.4$ Hz, 1H), 1.96 (t, $J = 7.8$ Hz, 2H), 1.64 (s, 3H), 1.56–1.50 (m, 1H), 1.43–1.31 (m, 3H), 0.84 (s, 9H), 0.01 ppm (d, $J = 3.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 145.2$, 109.9, 71.5, 67.2, 37.6, 32.3, 25.7, 23.4, 22.1, 18.1, −5.4, −5.5 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3566$ (O−H), 3074, 2955, 2931, 2858, 1647 cm^{-1} (C=C); LRMS (EI): m/z: 258 $[M]^+$ (1), 201 (22), 183 (4), 133 (4), 131 (6), 109 (100), 105 (23); HRMS (EI): calcd for $C_{14}H_{30}O_2Si$: 258.2015; found: 258.2014.

Compound 14: Imidazole (5.39 g, 79.31 mmol) and TBDPSCl (16.6 mL, 63.8 mmol) were added to a solution of alcohol **13** (13.80 g, 53.48 mmol) in DMF (10 mL) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with MeOH. Water was added. The mixture was extracted with 20% Et_2O in hexane. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to give the crude product as a pale-yellow oil, which was used in the next step without further purification.

The residue thus obtained was dissolved in MeOH (125 mL). PPTS (4.03 g, 16.03 mmol) was added at room temperature. The resulting mixture was stirred for 4 d at room temperature. Then H_2O was added and the reaction mixture was extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 5–10% EtOAc in hexane to afford **14** (17.15 g, 84% yield over 2 steps) as a pale-yellow oil. R_f: 0.32 (10% EtOAc/hexane); $[\alpha]_D^{20} = +12.3$ ($c = 2.02$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.83$–7.78 (m, 4H), 7.49–7.45 (m, 6H), 4.73 (s, 1H), 4.65 (s, 1H), 3.90 (m, 1H), 3.60 (m, 2H), 2.15 (br s, 1H), 1.93 (t, $J = 7.3$ Hz, 2H), 1.71 (s, 3H), 1.62–1.41 (m, 4H), 1.19 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 145.2$, 135.8, 135.6, 134.0, 133.8, 129.67, 129.66, 127.6, 127.5, 109.9, 73.9, 65.9, 37.5, 33.1, 27.0, 23.0, 22.2, 19.3 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3588$ (O−H), 3074, 2934, 2860, 1648 (C=C), 1472, 1463, 1428 cm^{-1}; LRMS (EI): m/z: 325 $[M-C_4H_9]^+$ (100), 200 (8), 199 (45), 139 (9), 109 (55); HRMS (EI): m/z: calcd for $C_{20}H_{25}O_2Si$: 325.1638 $[M-C_4H_9]^+$; found: 325.1624.

Compound 15: DMSO (6.6 mL, 93.0 mmol) was added to a solution of oxalyl chloride (6.1 mL, 69.9 mmol) in CH_2Cl_2 (700 mL) at −78 °C. The mixture was stirred for 15 min. Alcohol **14** (17.79 g, 46.49 mmol) in CH_2Cl_2 (200 mL) was added at −78 °C. The mixture was stirred for 30 min. iPr$_2$NEt (50.0 mL, 287.0 mmol) was added at −78 °C. The result-

ing mixture was stirred for 10 min at −78 °C. Finally, the reaction was quenched with phosphate buffer (pH 7) and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 3% EtOAc in hexane to afford aldehyde **15** (16.45 g, 93%) as a pale-yellow oil. R_f: 0.64 (10% EtOAc in hexane); $[\alpha]_D^{20} = -6.43$ ($c = 3.92$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.60$ (d, $J = 1.6$ Hz, 1H), 7.68–7.64 (m, 4H), 7.47–7.36 (m, 6H), 4.69 (s, 1H), 4.61 (s, 1H), 4.06 (dt, $J = 5.7$, 1.6 Hz, 1H), 1.92 (t, $J = 7.4$ Hz, 2H), 1.66 (s, 3H), 1.63–1.40 (m, 4H), 1.14 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 203.5$, 144.9, 135.8, 135.7, 133.2, 133.1, 130.0, 129.9, 127.78, 127.75, 110.3, 78.0, 37.5, 32.3, 27.0, 22.2, 22.0, 19.3 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3076$, 3058, 2938, 2865, 1735 (C=O), 1649 (C=C), 1590, 1466, 1431 cm^{-1}; LRMS (EI): *m/z*: 380 $[M]^+$ (2), 323 (53), 305 (14), 267 (15), 245 (24), 229 (18), 199 (100), 139 (38), 107 (69); HRMS (EI): *m/z*: calcd for $C_{24}H_{32}O_2Si$: 380.2172; found: 380.2167.

Compound 16 from 15: $ClMg(CH_2)_3OMgCl$ (300 mL, 90.0 mmol, 0.3 M in THF) was added to a solution of aldehyde **15** (16.45 g, 43.31 mmol) in THF (150 mL) at −78 °C.[31] The resulting mixture was stirred for 2 h at −78 °C. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 20–40% EtOAc in hexane to afford diol **16** (17.30 g, 91%) in the form of a pale-yellow oil as a mixture of diastereomers.

Compound 16 from 20: DIBAL-H (1 M in hexane, 11.8 mL, 11.8 mmol) was added to a solution of **20** (1.67 g, 3.58 mmol) in CH_2Cl_2 (15 mL) at −40 °C. The resulting mixture was stirred for 4 h from −40 °C to room temperature. The reaction was quenched with H_2O at −78 °C slowly and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 20–40% EtOAc in hexane to afford a pale-yellow oil **16** (1.10 g, 70%) as a mixture of diastereomers. R_f: 0.31 (35% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): *m/z*: $\delta =$ 7.70–7.66 (m, 4H), 7.44–7.26 (m, 6H), 4.62–4.51 (m, 2H), 3.61–3.56 (m, 4H), 2.55 (br s, 2H), 1.85–1.65 (m, 2H), 1.65–1.15 (m, 11H), 1.08 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 145.5$, 135.97, 135.93, 135.8, 133.8, 133.77, 133.74, 133.4, 129.8, 129.7, 127.7, 127.6, 127.5, 76.6, 76.5, 74.7, 73.2, 62.9, 62.8, 37.6, 37.5, 32.6, 30.9, 30.3, 29.5, 29.4, 28.7, 27.0, 23.4, 22.9, 22.2, 22.1, 19.4, 19.3 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3614$ (O−H), 3430 (O−H), 3073, 2933, 2859, 1648 (C=C), 1488, 1472 cm^{-1}; LRMS (EI): *m/z*: 383 $[M-C_4H_9]^+$ (4), 365 (24), 305 (22), 199 (54), 167 (15), 150 (13); HRMS (EI): *m/z*: calcd for $C_{23}H_{31}O_3Si$: 383.2042 $[M-C_4H_9]^+$; found: 383.2031.

Compound 17: DMSO (13.0 mL, 183.1 mmol) was added to a solution of oxalyl chloride (12.0 mL, 137.5 mmol) in CH_2Cl_2 (700 mL) at −78 °C. The mixture was stirred for 15 min. Diol **16** (17.30 g, 39.43 mmol) in CH_2Cl_2 (200 mL) was added at −78 °C. The mixture was stirred for 30 min. iPr$_2$NEt (90.0 mL, 516.7 mmol) was added at −78 °C. The resulting mixture was stirred for 10 min at −78 °C. The reaction was quenched with phosphate buffer (pH 7) and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 5–10% EtOAc in hexane to afford ketoaldehyde **17** (15.49 g, 90%) as a pale-yellow oil. R_f: 0.83 (35% EtOAc in hexane); $[\alpha]_D^{20} = -8.01$ ($c = 11.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.70$ (s, 1H), 7.65–7.61 (m, 4H), 7.42–7.26 (m, 6H), 4.66 (s, 1H), 4.58 (s, 1H), 4.23 (app. t, $J = 5.9$ Hz, 1H), 2.88–2.47 (m, 4H), 1.87 (t, $J = 7.3$ Hz, 2H), 1.63 (s, 3H), 1.61–1.32 (m, 4H), 1.13 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 210.8$, 200.4, 145.2, 135.88, 135.84, 133.4, 133.0, 130.0, 129.9, 127.8, 127.7, 110.2, 79.0, 37.4, 36.9, 34.4, 30.7, 27.0, 22.2, 22.1, 19.4 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3074$, 3044, 2934, 1715 (ketone, aldehyde C=O), 1650 (C=C), 1589, 1472, 1428 cm^{-1}; LRMS (EI): *m/z*: 436 $[M]^+$ (2), 379 (25), 361 (31), 301 (39), 285 (30), 279 (22), 245 (17), 199 (100), 163 (58), 145 (74), 139 (35); HRMS (EI): *m/z*: calcd for $C_{27}H_{36}O_3Si$: 436.2434; found: 436.2428.

Compound 18: 2-Methyl-2-butene (20.0 mL, 188.7 mmol) and NaH_2PO_4 (21.00 g, 134.66 mmol) were added to a solution of aldehyde **17** (15.49 g, 35.33 mmol) in tBuOH (75 mL) and H_2O (75 mL). The mixture was stirred for 5 min at 0 °C. $NaClO_2$ (12.00 g, 132.73 mmol) was added. The resulting mixture was stirred overnight at room temperature and then brine was added. The mixture was acidified to pH 4 by dilute HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography, eluting with 0.1% AcOH in 10–30% EtOAc/hexane to afford acid **18** (14.16 g, 88%) as a pale-yellow oil. R_f: 0.30 (20% EtOAc in hexane); $[\alpha]_D^{20} = -10.2$ ($c = 6.65$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.65$–7.60 (m, 4H), 7.45–7.36 (m, 6H), 4.65 (s, 1H), 4.56 (s,1H), 4.22 (t, $J = 5.8$ Hz, 1H), 2.84 (dt, $J = 19.4$, 6.5 Hz, 1H), 2.72 (dt, $J = 19.1$, 6.5 Hz, 1H), 2.56–2.38 (m, 2H), 1.84 (t, $J = 7.5$ Hz, 2H), 1.62 (s, 3H), 1.58–1.18 (m, 4H), 1.13 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 210.9$, 178.6, 145.1, 135.85, 135.83, 133.5, 132.9, 130.0, 129.9, 127.8, 127.7, 110.2, 78.9, 37.4, 34.4, 32.8, 27.3, 27.0, 22.2, 22.1, 19.4 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3503$ (acid O−H), 3073, 2933, 2860, 1751 (acid C=O), 1713 (ketone C=O), 1648 (C=C), 1589, 1472, 1463 cm^{-1}; LRMS (EI): *m/z*: 395 $[M-C_4H_9]^+$ (11), 377 (3), 349 (18), 317 (15), 299 (24), 261 (11), 223 (23), 199 (100), 179 (68), 161 (60); HRMS (EI): *m/z*: calcd for $C_{23}H_{27}O_4Si$: 395.1679 $[M-C_4H_9]^+$; found: 395.1665.

Compounds 19 and 20: NEt_3 (0.235 mL, 1.69 mmol) and iBuOCOCl (0.220 mL, 1.69 mmol) were added to a solution of acid **18** (0.3850 g, 0.8480 mmol) in THF (10 mL) and Et_2O (10 mL). The mixture was stirred for 2 h at room temperature and filtered through sintered glass by cannula under Ar. CH_2N_2 in Et_2O (15 mL, 6.0 mmol) was added at 0 °C. The resulting mixture was stirred for 6 h at 0 °C. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 10–20% EtOAc in hexane to afford diazoketone **19** (0.2670 g, 66%) as a pale-yellow oil and ester **20** (0.0992 g, 20%) as a pale-yellow oil.

Compound 19: R_f: 0.50 (20% EtOAc in hexane); $[\alpha]_D^{20} = -21.8$ ($c = 5.34$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.64$–7.60 (m, 4H), 7.44–7.40 (m, 2H), 7.38–7.35(m, 4H), 5.21 (br s, 1H), 4.65 (s, 1H), 4.56 (s, 1H), 4.21 (t, $J = 5.9$ Hz, 1H), 2.84 (dt, $J = 19.0$, 6.5 Hz, 1H), 2.77 (dt, $J = 19.0$, 6.6 Hz, 1H), 2.43 (br s, 1H), 2.39 (br s, 1H), 1.85 (t, $J = 7.9$ Hz, 2H), 1.62 (s, 3H), 1.64–1.51 (m, 2H), 1.47–1.40 (m, 1H), 1.35–1.31 (m, 1H), 1.11 ppm (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 211.1$, 193.2, 145.1, 135.8, 135.7, 133.4, 133.0, 129.9, 127.7, 127.6, 110.1, 78.9, 54.3 (br), 37.4, 34.4, 33.5, 32.8, 27.0, 22.2, 22.1, 19.3 ppm; IR (CH_2Cl_2): $\tilde{\nu} =$ 3073, 2932, 2108 (N≡N), 1734 (diazoketone C=O), 1717 (ketone C=O), 1646 (C=C), 1559, 1472 cm^{-1}; LRMS (EI): *m/z*: 419 $[M^+-C_4H_9]$ (6), 393 (26), 392 (88), 389 (26), 200 (17), 199 (100), 157 (11); HRMS (EI): *m/z*: calcd for $C_{24}H_{27}N_2O_3Si$: 419.1791 $[M-C_4H_9]^+$; found: 419.1780.

Compound 20: R_f (10% EtOAc in hexane): 0.53; $[\alpha]_D^{20} = -8.95$ ($c = 2.48$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.66$–7.60 (m, 4H), 7.40–7.37 (m, 6H), 4.65 (s, 1H), 4.57 (s, 1H), 4.21 (t, $J = 5.8$ Hz, 1H), 3.65 (s, 3H), 2.90–2.72 (m, 2H), 2.51–2.35 (m, 2H), 1.85 (t, $J = 7.4$ Hz, 2H), 1.62 (s, 3H), 1.66–1.25 (m, 4H), 1.12 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 210.9$, 173.1, 145.2, 135.88, 135.83, 133.5, 133.0, 129.98, 129.95, 127.8, 127.7, 110.2, 79.0, 51.7, 37.4, 34.3, 33.1, 27.2, 27.0, 22.2, 22.1, 19.4 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3073$, 2954, 2933, 2859, 1735 (ester C=O), 1718 (ketone C=O), 1648 (C=C), 1589, 1472, 1463 cm^{-1}; LRMS (EI): *m/z*: 409 $[M-C_4H_9]^+$ (16), 391 (8), 353 (8), 331 (6), 279 (5), 237 (11), 199 (12), 193 (35), 179 (13), 161 (100); HRMS (EI): *m/z*: calcd for $C_{24}H_{29}O_4Si$: 409.1835 $[M-C_4H_9]^+$; found: 409.1835.

Compounds 21 to 23: To a solution of diazoketone **19** (0.4980 g, 1.046 mmol) in CH_2Cl_2 (105 mL) was added powdered, predried 4 Å molecular sieves (0.4906 g). The mixture was stirred for 5 min at 0 °C. [Rh_2(Oct)$_4$] (0.0047 g, 0.006 mmol) was added. The resulting mixture was stirred for 3 h at 0 °C and filtered through sintered glass. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 2–4% EtOAc in hexane to afford ketone **21** (0.2859 g, 61%) as a white solid, ketone **22** (0.0936 g, 20%) as a white solid, and **23** (0.0234 g, 5%) as a colorless oil.

Compound 21: R_f: 0.30 (10% EtOAc in hexane); m.p. 109–112 °C; $[\alpha]_D^{20} = -27.8$ ($c = 2.40$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.74$–7.72 (m, 4H), 7.45–7.36 (m, 6H), 4.33 (dd, $J = 9.3$, 3.5 Hz, 1H), 3.62 (dd, $J = 11.7$, 4.9 Hz, 1H), 2.68–2.54 (m, 2H), 2.30 (m, 1H), 2.07 (dd, $J = 13.2$, 9.4 Hz, 1H), 1.75 (qd, $J = 12.6$, 3.4 Hz, 1H), 1.63–1.48 (m, 4H), 1.43–1.35 (m, 1H), 1.23 (m, 1H), 1.15–1.05 (m, 1H), 1.05 (s, 9H), 0.97 ppm (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.5, 135.9, 135.7, 134.3, 133.5, 129.7, 129.5, 127.6, 127.3, 84.6, 78.4, 74.2, 45.0, 43.7, 38.2, 32.8, 30.8, 27.0, 23.1, 21.0, 19.7, 19.4 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 2960, 2860, 1731 (ketone C=O), 1472, 1428, 1308 cm^{-1}; LRMS (EI): *m*/*z*: 391 $[M-C_4H_9]^+$ (100), 373 (10), 363 (6), 313 (22), 199 (29), 147 (19); HRMS (EI): *m*/*z*: calcd for $C_{24}H_{27}O_3Si$: 391.1729 $[M-C_4H_9]^+$; found: 391.1728; 99% *ee* which was determined by using an OD chiralcel column, eluting with 3% isopropanol in hexane at 0.5 mL min^{-1}.

X-ray crystallography: Data were recorded by using a MAR diffractometer with a 300 mm image plate detector by using graphite monochromatized $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). The crystal was mounted on a glass capillary. The structure was solved by direct methods employing SIR-97 program on PC. Most non-H atoms were located according to the direct methods and successive least-square Fourier cycles. Positions of other non-hydrogen atoms were found after successful refinement by full-matrix least-squares by using program SHELXL-97 on PC.

*X-ray crystallographic data for (±)-**21***: $C_{28}H_{36}O_3$ Si; F_w: 448.66 g mol^{-1}; crystal size: 0.50 × 0.40 × 0.20 mm; monoclinic; $P2_1/n$ (#14); a = 10.376(2), b = 7.990(2), c = 30.543(6) Å; β = 93.91(3)°; V = 2526.3(9) Å^3, Z = 4, ρ_{calcd} = 1.180 g cm^{-3}; $\mu(Mo_{K\alpha})$ = 0.119 mm^{-1}; $F(000)$ = 968; T = 301 K; 4063 reflections collected; 2206 independent reflections; 1212 reflections with $F_0 > 4\sigma(F_0)$; $2\theta_{max}$ = 50.60°; 293 variable parameters by full-matrix least-squares refinement on F^2 reaches to R_1 = 0.0375 and wR_2 = 0.0746; S = 0.779, largest diff. peak and hole: 0.137/−0.153e Å^{-3}.

CCDC-645998 contains the supplementary crystallographic data for (±)-**21**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif/.

Compound 22: R_f: 0.33 (10% EtOAc in hexane); m.p. 119–122 °C; $[\alpha]_D^{20}$ = +8.48 (c = 0.33 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.64 (m, 4H), 7.46–7.41 (m, 2H), 7.40–7.35 (m, 4H), 4.14 (dd, J = 9.1, 3.2 Hz, 1H), 3.89 (t, J = 2.6 Hz, 1H), 2.41–2.31 (m, 2H), 2.29–2.24 (m, 1H), 2.06 (dd, J = 13.4, 9.1 Hz, 1H), 1.93–1.88 (m, 1H), 1.76–1.69 (m, 1H), 1.61–1.53 (m, 3H), 1.50 (m, 2H), 1.43 (s, 3H), 1.33–1.29 (m, 1H), 1.09 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.5, 136.2, 136.1, 134.0, 133.1, 129.8, 129.7, 127.7, 127.5, 82.7, 78.9, 74.2, 45.1, 42.8, 39.4, 31.9, 29.3, 29.2, 27.2, 21.4, 19.5, 16.9 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 2935, 2859, 1732 (ketone C=O), 1472, 1427, 1274, 1265, 1255 cm^{-1}; LRMS (EI): *m*/*z*: 391 $[M-C_4H_9]^+$ (100), 373 (14), 313 (15), 253 (5), 200 (10), 199 (69), 147 (16), 139 (13); HRMS (EI): *m*/*z*: calcd for $C_{24}H_{27}O_3Si$: 391.1729 $[M-C_4H_9]^+$; found: 391.1727.

Compound 23: R_f: 0.33 (10% EtOAc in hexane); $[\alpha]_D^{20}$ = +31.8 (c = 2.54 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78–7.70 (m, 4H), 7.44–7.35 (m, 6H), 4.29 (dd, J = 8.9, 5.0 Hz, 1H), 4.24 (dd, J = 11.0, 5.3 Hz, 1H), 2.75–2.60 (m, 2H), 2.29 (dd, J = 16.4, 5.9 Hz, 1H), 1.95 (dd, J = 12.7, 8.9 Hz, 1H), 1.60–1.46 (m, 5H), 1.42–1.35 (m, 2H), 1.31–1.23 (m, 1H), 1.07 (s, 9H), 0.82 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.5, 136.2, 135.8, 134.9, 133.5, 129.6, 129.5, 127.5, 127.4, 84.9, 78.1, 71.9, 45.7, 40.6, 33.9, 31.4, 30.0, 26.9, 22.4, 20.2, 19.4, 19.3 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 2959, 2859, 1731 (ketone C=O), 1473, 1428, 1274, 1266, 1255 cm^{-1}; LRMS (EI): *m*/*z*: 391 $[M-C_4H_9]^+$ (100), 373 (16), 313 (30), 253 (10), 199 (47), 183 (12), 175 (18), 139 (13); HRMS (EI): *m*/*z*: calcd for $C_{24}H_{27}O_3Si$: 391.1729 $[M-C_4H_9]^+$; found: 391.1732.

Compound (−)-24: 1,2-Bistrimethylsiloxyethane (1.0 mL, 4.0 mmol) was added to a solution of ketone **22** (0.2946 g, 0.6189 mmol) in CH_2Cl_2 (10 mL) at room temperature. TMSOTf (0.010 mL, 0.055 mmol) was added. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 10% EtOAc in hexane to afford the desired ketal (0.2849 g, 93%) as a colorless oil. R_f: 0.46 (20% EtOAc in hexane); $[\alpha]_D^{20}$ = −0.06 (c = 8.30 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.67 (m, 4H), 7.43–7.34 (m, 6H), 4.00–3.82 (m, 6H), 2.41–2.33 (m, 1H), 2.05–1.96 (m, 1H), 1.85–1.62 (m, 4H), 1.54–1.41 (m, 5H), 1.37 (s, 3H), 1.21–1.16 (m, 1H), 1.10 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.2, 136.1, 134.5, 133.3, 129.6, 129.5, 127.5, 127.3, 106.9, 82.2, 75.8, 74.4, 64.8, 64.6, 44.8, 42.2, 40.9, 30.9, 29.0, 27.8, 27.2, 21.2, 19.5, 16.8 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 2935, 2895, 2859, 1589, 1473, 1464, 1450, 1429 cm^{-1}; LRMS (EI): *m*/*z*: 492 $[M]^+$ (13), 435 (65), 393 (69), 313 (38), 305 (34), 219 (35), 199 (100), 197 (35), 193 (41), 135 (41); HRMS (EI): *m*/*z*: calcd for $C_{30}H_{40}O_4Si$: 492.2695; found: 492.2691.

TBAF (1 M, 17.0 mL, 17.0 mmol) was added to a solution of this ketal (0.8339 g, 1.692 mmol) in THF (3 mL). The resulting mixture was refluxed for 40 h. Brine was added. The mixture was acidified to pH 5 by dilute HCl and extracted with EtOAc. The combined organic layers were washed with H_2O twice and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to give the crude product as a pale-yellow oil, which was used in the next reaction without further purification.

DMSO (0.60 mL, 8.45 mmol) was added to a solution of oxalyl chloride (0.50 mL, 5.73 mmol) in CH_2Cl_2 (25 mL) at −78 °C. The mixture was stirred for 15 min. The crude product in CH_2Cl_2 (10 mL) was added at −78 °C. The mixture was stirred for 30 min. NEt_3 (2.0 mL, 14.3 mmol) was added at −78 °C. The resulting mixture was stirred at −78 °C for 10 min. The reaction was quenched with H_2O and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 35% EtOAc in hexane to afford ketone (−)-**24**. (0.3479 g, 82% yield over 2 steps) as a white solid. R_f: 0.39 (35% EtOAc in hexane); m.p. 59–62 °C; $[\alpha]_D^{20}$ = −9.76 (c = 3.72 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.06 (dt, J = 8.0, 1.9 Hz, 1H), 3.98–3.75 (m, 4H), 2.67 (ddd, J = 13.7, 9.9, 6.4 Hz, 1H), 2.11 (dtd, J = 13.7, 5.1, 1.1 Hz, 1H), 1.97–1.71 (m, 7H), 1.66–1.52 (m, 2H), 1.41–1.34 (m, 1H), 1.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.5, 106.2, 85.8, 78.5, 64.7, 64.6, 50.4, 43.1, 40.2, 38.0, 27.2, 24.3, 23.0, 20.4 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3061, 2962, 2889, 1714 (ketone C=O), 1447 cm^{-1}; LRMS (EI): *m*/*z*: 252 $[M]^+$ (4), 237 (5), 225 (1), 224 (13), 211 (1), 210 (13), 209 (100), 165 (1); HRMS (EI): *m*/*z*: calcd for $C_{14}H_{20}O_4$: 252.1361; found: 252.1368.

Compounds 26 and 27: TBAF (1 M, 3.2 mL, 3.2 mmol) was added to a solution of ketone **21** (0.4800 g, 1.071 mmol) in THF (6 mL). The resulting mixture was stirred overnight at room temperature. Brine was added. The mixture was acidified to pH 5 by dilute HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 30–50% EtOAc in hexane to afford the desired alcohol (0.2016 g, 90%) as a white solid. R_f: 0.39 (50% EtOAc in hexane); m.p. 88–90 °C; $[\alpha]_D^{20}$ = −22.6 (c = 1.02 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (dd, J = 9.2, 3.2 Hz, 1H), 3.38 (dd, J = 11.3, 5.1 Hz, 1H), 2.73 (brs, 1H), 2.55–2.47 (m, 1H), 2.41–2.25 (m, 2H), 2.02 (dd, J = 13.3, 9.2 Hz, 1H), 1.78–1.66 (m, 2H), 1.54–1.38 (m, 4H), 1.32–1.24 (m, 2H), 1.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 84.3, 78.3, 71.5, 44.3, 44.0, 38.6, 32.2, 30.9, 23.8, 20.9, 19.9 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3580 (O−H), 2063, 2942, 2866, 1732 cm^{-1} (ketone C=O); LRMS (EI): *m*/*z*: 210 $[M]^+$ (54), 182 (70), 167 (55), 166 (61), 136 (26), 111 (100), 107 (50), 93 (61); HRMS (EI): *m*/*z*: calcd for $C_{12}H_{18}O_3$: 210.1255; found: 210.1255.

Imidazole (0.7788, 11.43 mmol) and TBSCl (0.8615 g, 5.715 mmol) were added to a solution of this deprotected alcohol (0.2016 g, 0.9600 mmol) in DMF (0.500 mL). The resulting mixture was stirred for 64 h at room temperature. The reaction was quenched with H_2O and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 7% EtOAc in hexane to afford ketone **26** (0.2697 g, 87%) as a white solid. R_f: 0.30 (10% EtOAc in hexane); m.p. 65–66 °C; $[\alpha]_D^{20}$ = −36.7 (c = 2.76 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.29 (dd, J = 9.3, 3.6 Hz, 1H), 3.63 (dd, J = 9.0, 7.5 Hz, 1H), 2.56 (dt, J = 16.3, 8.6 Hz, 1H), 2.43–2.38 (m, 1H), 2.30 (ddd, J = 16.3, 6.7, 4.4 Hz, 1H), 2.09 (dd, J = 13.3, 9.4 Hz, 1H), 1.76–1.66 (m, 3H), 1.61–1.53 (m, 3H), 1.44–1.37 (m, 1H), 1.34–1.30 (m, 1H), 1.14 (s, 3H), 0.91 (s, 9H), 0.10 ppm (d, J = 2.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.3, 84.4, 78.3, 73.1, 44.9, 43.8, 38.2, 32.8, 30.9, 25.9, 23.2, 21.1, 19.7, 18.1, −3.6, −5.0 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 2958, 2932, 2858, 1732 (ketone C=O), 1472, 1276, 1254 cm^{-1}; LRMS (EI): *m*/*z*: 309 $[M-CH_3]^+$ (3), 268 (23), 267 (100), 249 (20), 239 (17), 169 (9), 147 (29), 129 (15), 123 (12), 105 (12); HRMS (EI): *m*/*z*: calcd for $C_{17}H_{29}O_3Si$: 309.1886 $[M-CH_3]^+$; found: 309.1884.

To a solution of the deprotected alcohol (0.0650 g, 0.3091 mmol) in CH_2Cl_2 (5 mL) was added *i*Pr_2NEt (0.60 mL, 3.43 mmol) and MOMCl

(0.200 mL, 2.633 mmol). The resulting mixture was stirred overnight at room temperature. The reaction was quenched with H_2O and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 30% EtOAc in hexane to afford ketone **27** (0.0738 g, 94%) as a white solid. R_f: 0.55 (50% EtOAc in hexane); m.p. 42–45 °C; $[\alpha]_D^{20} = -7.98$ ($c = 5.75$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.83$ (d, $J = 7.1$ Hz, 1H), 4.65 (d, $J = 7.1$ Hz, 1H), 4.30 (dd, $J = 9.3$, 3.4 Hz, 1H), 3.53 (dd, $J = 11.6$, 5.0 Hz, 1H), 3.41 (s, 3H), 2.59–2.52 (m, 1H), 2.48–2.42 (m, 1H), 2.40–2.34 (m, 1H), 2.12 (dd, $J =$ 13.3, 9.3 Hz, 1H), 1.96–1.91 (m, 1H), 1.82–1.76 (dt, $J = 13.7$, 7.4 Hz, 1H), 1.70–1.55 (m, 4H), 1.43–1.34 (m, 2H), 1.17 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 210.3$, 96.0, 83.8, 79.0, 77.5, 56.0, 45.3, 44.0, 38.6, 32.7, 27.4, 23.9, 20.9, 20.0 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3055$, 2946, 2892, 1732 (ketone C=O), 1472, 1455 cm^{-1}; LRMS (EI): m/z: 254 $[M]^+$ (14), 210 (56), 191 (100), 165 (28), 149 (23), 137 (10), 119 (28); HRMS (EI): m/z: calcd for $C_{14}H_{22}O_4$: 254.1518; found: 254.1517.

Compound (+)-24: To a solution of ketone **21** (2.41 g, 5.08 mmol) in CH_2Cl_2 (22 mL) was added 1,2-bistrimethylsiloxyethane (2.7 mL, 11.0 mmol) at room temperature. TMSOTf (0.020 mL, 0.110 mmol) was added. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to give the crude product as a pale-yellow oil, which was used in the next reaction without further purification.

The residue was dissolved in TBAF (1 M, 42.0 mL, 42.0 mmol). The resulting mixture was stirred for 64 h at room temperature. Brine was added and the mixture was acidified to pH 5 by dilute HCl and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 50–90% EtOAc in hexane to afford the desired alcohol (1.27 g, 99%) as a white solid. R_f: 0.50 (EtOAc); m.p. 96–98 °C; $[\alpha]_D^{20} = -4.83$ ($c = 6.35$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.04$–3.77 (m, 5H), 3.31 (dd, $J = 11.2$, 5.0 Hz, 1H), 2.51 (td, $J = 13.8$, 7.2 Hz, 1H), 2.22 (br s, 1H), 2.00–1.61 (m, 5H), 1.51–1.20 (m, 6H), 1.08 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 106.6$, 84.0, 76.3, 71.9, 64.9, 64.7, 44.2, 44.0, 40.8, 31.4, 27.5, 26.5, 21.2, 20.3 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3576$ (O–H), 3469 (O–H), 2942, 2892, 1479, 1452 cm^{-1}; LRMS (EI): m/z: 254 $[M]^+$ (8), 209 (34), 155 (100), 153 (23), 136 (12), 111 (31), 109 (28); HRMS (EI): m/z: calcd for $C_{14}H_{22}O_4$: 254.1518; found: 254.1516.

DMSO (0.100 mL, 1.409 mmol) was added to a solution of oxalyl chloride (0.080 mL, 0.917 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The mixture was stirred for 15 min. The alcohol (0.0880 g, 0.3464 mmol) in CH_2Cl_2 (10 mL) was added at −78 °C. The mixture was stirred for 30 min. NEt_3 (0.30 mL, 2.15 mmol) was added at −78 °C. The resulting mixture was stirred for 10 min at −78 °C. The reaction was quenched with H_2O and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 35% EtOAc in hexane to afford ketone (+)-**24** (0.0853 g, 98%) as a white solid. All characterizations were identical to (−)-**24** except $[\alpha]_D^{20} = +0.07$ ($c = 9.52$ in $CHCl_3$).

Compound 28: To a mixture of methyltriphenylphosphonium bromide (6.46 g, 18.10 mmol) in THF (100 mL) was added *n*BuLi (1.6 M, 9.4 mL, 15.0 mmol) at 0 °C. The mixture was stirred for 30 min at room temperature. Ketone (+)-**24** (0.6899 g, 2.738 mmol) in THF (10 mL) was added. The resulting mixture was stirred for 5 h at room temperature. The reaction was quenched with H_2O (5 mL) and then HCl (3 M, 10 mL) was added. The resulting mixture was refluxed overnight. The mixture was basicified to pH 6 by saturated $NaHCO_3$ and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 7.5% EtOAc in hexane to afford ketone **28** (0.5580 g, 95%) as a white solid. R_f: 0.19 (10% EtOAc in hexane); m.p. 69–72 °C; $[\alpha]_D^{20} = +20.0$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.01$ (s, 1H), 4.93 (s, 1H), 4.26 (d, $J = 8.8$ Hz, 1H), 2.58–2.48 (m, 1H), 2.44–2.37 (m, 2H), 2.32–2.24 (m, 1H), 2.20–2.14 (m, 3H), 1.75–1.56 (m, 3H), 1.50–1.35 (m, 2H), 1.13 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 208.1$, 148.0, 112.4, 84.5, 80.0, 46.0, 44.1, 39.9, 32.2, 31.3, 28.8, 22.5, 21.5 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3060$, 2939, 2858, 1730 (ketone C=O), 1641 (C=C), 1445 cm^{-1}; LRMS (EI): m/z: 206 $[M]^+$ (34), 191 (12), 188 (6), 164 (10), 163 (73), 162 (100), 161 (5), 135 (6), 134 (8); HRMS (EI): m/z: calcd for $C_{13}H_{18}O_2$: 206.1306; found: 206.1306.

Compound 29: Ketone **28** (0.4406 g, 2.138 mmol) in THF (20 mL) was added to a solution of LDA (8.5 mmol) in THF (400 mL) at −78 °C. The mixture was stirred for 1 h at −78 °C. Mander's reagent (0.850 mL, 10.7 mmol) was added at −78 °C. The resulting mixture was stirred for 2 h at −78 °C. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 3% EtOAc in hexane to afford ester **29** (0.4986 g, 88%) as a colorless oil. R_f: 0.30 (4% EtOAc in hexane); $[\alpha]_D^{20} = -32.5$ ($c = 2.20$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 11.58$ (br s, 1H), 4.97 (s, 1H), 4.95 (s, 1H), 4.38 (d, $J = 7.3$ Hz, 1H), 3.76 (s, 3H), 2.57–2.43 (m, 3H), 2.19–2.13 (m, 2H), 1.92 (d, $J = 12.4$ Hz, 1H), 1.85–1.70 (m, 1H), 1.65–1.50 (m, 1H), 1.37–1.16 (m, 2H), 1.07 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.8$, 172.1, 149.1, 110.8, 93.1, 86.1, 73.7, 51.5, 46.5, 46.0, 38.1, 29.3, 28.4, 25.1, 18.7 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3090$, 2954, 2920, 2871, 1750 (ester C=O), 1730, 1667, 1645 (C=C), 1626, 1444 cm^{-1}; LRMS (EI): m/z: 264 $[M]^+$ (17), 246 (12), 231 (5), 141 (5), 125 (9), 124 (100), 109 (15); HRMS (EI): m/z: calcd for $C_{15}H_{20}O_4$: 264.1361; found: 264.1356.

Compound 30: Ester **29** (0.2739 g, 1.0375 mmol) in THF (50 mL) was added to a solution of NaH (0.1605 g, 6.6875 mmol) in THF (150 mL) at room temperature. The mixture was stirred for 1 h at room temperature. MeI (1.5 mL, 23.8 mmol) was added. The resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with H_2O and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 5% EtOAc in hexane to afford ester **30** (0.2336 g, 81%) as a colorless oil. R_f: 0.38 (10% EtOAc in hexane); $[\alpha]_D^{20} = +44.6$ ($c = 0.92$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.10$ (s, 1H), 4.97 (s, 1H), 4.45 (dd, $J = 9.1$, 3.7 Hz, 1H), 3.74 (s, 3H), 2.55 (d, $J = 14.7$, 1H), 2.51–2.45 (m, 1H), 2.27 (d, $J = 14.7$ Hz, 1H), 2.19 (dt, $J = 13.1$, 4.1 Hz, 1H), 2.12 (dd, $J = 13.2$, 9.2 Hz, 1H), 1.84 (dd, $J =$ 13.2, 3.7 Hz, 1H), 1.71–1.65 (m, 2H), 1.55 (s, 3H), 1.55–1.46 (m, 1H), 1.41–1.37 (m, 1H), 1.10 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 207.2, 173.4, 148.3, 112.4, 84.6, 78.8, 52.8, 52.7, 46.9, 42.0, 39.0, 34.7, 32.0, 26.0, 23.8, 19.5 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3093$, 2996, 2940, 2865, 1745 (ester C=O), 1726 (ketone C=O), 1643 cm^{-1} (C=C); LRMS (EI): m/z: 278 $[M]^+$ (26), 235 (8), 207 (13), 206 (21), 175 (20), 150 (24), 148 (13), 147 (100), 124 (16), 122 (11), 107 (10); HRMS (EI): m/z: calcd for $C_{16}H_{22}O_4$: 278.1518; found: 278.1513.

Compound 31: SmI_2 in THF (0.1 M 200.0 mL, 20.0 mmol) was added quickly in one portion at 0 °C to a solution of ester **30** (0.4570 g, 1.6438 mmol) in THF (600 mL) by using an addition funnel. The mixture was stirred for 1 h at 0 °C. The reaction was quenched with 0.5 M HCl and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 15% EtOAc in hexane to afford hemiacetal **31** (0.4185 g, 91%) as a pale-yellow solid. R_f: 0.28 (20% EtOAc in hexane); m.p. 63–66 °C; $[\alpha]_D^{20} = +26.0$ ($c = 2.63$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.88$ (s, 1H), 4.70 (s, 1H), 3.74 (s, 3H), 2.80 (d, $J = 13.7$ Hz, 1H), 2.49 (td, $J = 13.0$, 5.5 Hz, 1H), 2.32 (td, $J = 13.6$, 6.5 Hz, 1H), 2.14–2.11 (m, 1H), 1.99 (td, $J = 13.6$, 6.5 Hz, 1H), 1.91 (d, $J = 13.7$ Hz, 1H), 1.77 (ddd, $J = 13.7$, 6.0, 1.4 Hz, 1H), 1.68–1.52 (m, 3H), 1.34 (s, 3H), 1.31 (ddd, $J = 14.5$, 6.5, 1.3 Hz, 1H), 1.01 (m, 1H), 0.77 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 175.0$, 148.2, 108.8, 103.4, 84.6, 53.5, 52.2, 37.8, 37.2, 33.4, 32.6, 32.3, 30.9, 23.8, 23.2, 21.6 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3414$ (O–H), 2944, 2871, 1727 (ester C=O), 1648 cm^{-1} (C=C); LRMS (EI): m/z: 280 $[M]^+$ (3), 262 (4), 234 (14), 207 (75), 175 (16), 151 (14), 148 (24), 147 (100); HRMS (EI): m/z: calcd for $C_{16}H_{24}O_4$: 280.1670; found: 280.1674.

Compound 32: *i*Pr_2NEt (15 mL, 85.8 mmol) and MOMCl (6.0 mL, 78.9 mmol) were added to a solution of hemiacetal **31** (0.4185 g, 1.4946 mmol) in CH_2Cl_2 (7 mL). The resulting mixture was stirred for

156 h at room temperature. The reaction was quenched with H_2O and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 5% EtOAc in hexane to afford ester **32** (0.4461 g, 92%) as a pale-yellow oil. R_f: 0.70 (20% EtOAc in hexane); $[\alpha]_D^{20} = -119$ ($c = 1.64$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.13$ (d, $J = 6.8$ Hz, 1H), 4.83 (s, 1H), 4.73 (d, $J = 6.8$ Hz, 1H), 4.67 (s, 1H), 3.70 (s, 3H), 3.40 (s, 3H), 2.75 (d, $J = 13.6$ Hz, 1H), 2.45 (td, $J = 12.7$, 5.7 Hz, 1H), 2.31–2.18 (m, 2H), 2.12–2.07 (m, 1H), 1.87 (d, $J = 13.6$ Hz, 1H), 1.77–1.47 (m, 4H), 1.29 (s, 3H), 1.30–1.23 (m, 1H), 0.99–0.94 (m, 1H), 0.74 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.5$, 148.3, 108.6, 106.1, 91.6, 85.6, 55.3, 55.2, 52.0, 38.3, 37.3, 33.5, 32.7, 32.3, 28.3, 24.7, 23.2, 21.7 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 2947$, 1726 (ester C=O), 1651 cm^{-1} (C=C); LRMS (EI): m/z: 324 $[M]^+$ (19), 279 (48), 261 (34), 229 (34), 219 (72), 207 (76), 201 (44), 161 (31), 147 (100); HRMS (EI): m/z: calcd for $C_{18}H_{28}O_5$: 324.1936; found: 324.1926.

Compound 33: To a solution of ester **32** (0.4461 g, 1.3768 mmol) in Et_2O (20 mL) was added LAH (0.3262 g, 8.5842 mmol) at room temperature. The resulting mixture was stirred for 4 h at room temperature. The reaction was quenched with H_2O at −78°C, slowly warmed to room temperature, and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was used in the next step without further purification.

To a solution of oxalyl chloride (0.500 mL, 5.731 mmol) in CH_2Cl_2 (100 mL) at −78°C was added DMSO (0.500 mL, 7.045 mmol). The mixture was stirred for 15 min. The crude product in CH_2Cl_2 (50 mL) was added at −78°C. The mixture was stirred for 30 min. NEt_3 (2.0 mL, 14.3 mmol) was added at −78°C. The resulting mixture was stirred for 10 min at −78°C. The reaction was quenched with H_2O and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to give the crude product as a pale-yellow oil, and the residue was used in the next step without further purification.

Compound 34: 60% NaH (0.2858 g, 7.145 mmol) was added to a solution of dimethyl (3-methyl-2-oxobutyl)phosphonate (1.45 g, 7.51 mmol) in THF (20 mL) at room temperature. The mixture was stirred for 30 min at room temperature. Crude **33** in THF (20 mL) was added. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with H_2O and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 5% EtOAc in hexane to afford ketone **34** (0.4475 g, 90% yield over 3 steps) as a colorless oil. R_f: 0.50 (10% EtOAc in hexane); $[\alpha]_D^{20} = -88.1$ ($c = 1.71$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.05$ (d, $J = 16.0$ Hz, 1H), 6.28 (d, $J = 16.0$ Hz, 1H), 5.11 (d, $J = 6.7$ Hz, 1H), 4.85 (s, 1H), 4.69 (d, $J = 6.7$ Hz, 1H), 4.68 (s, 1H), 3.38 (s, 3H), 2.84 (septet, $J = 6.8$ Hz, 1H), 2.49 (td, $J = 12.0$, 5.9 Hz, 1H), 2.32–2.18 (m, 2H), 2.15–2.09 (m, 2H), 1.93 (d, $J = 13.3$ Hz, 1H), 1.66–1.43 (m, 4H), 1.34–1.26 (m, 1H), 1.13 (s, 3H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.11 (d, $J = 6.8$ Hz, 3H), 1.05–6.97 (m, 1H), 0.72 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 203.8$, 149.4, 148.3, 126.9, 108.4, 107.1, 91.8, 86.0, 55.6, 50.1, 39.4, 38.7, 37.1, 33.5, 32.7, 32.4, 28.0, 25.8, 23.2, 21.7, 18.5, 18.4 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3085$, 2973, 1693 (enone C=O), 1668 (C=C), 1654 cm^{-1} (C=C); LRMS (EI): m/z: 362 $[M]^+$ (4), 317 (37), 299 (100), 281 (21), 259 (15), 245 (43), 229 (45); HRMS (EI): m/z: calcd for $C_{22}H_{34}O_4$: 362.2457; found: 362.2443.

(−)-Indicol (1): Ketone **34** (0.4475 g, 1.2361 mmol) in THF (40 mL) was added to a solution of $[Ph_3P(CuH)]_6$ (1.0569 g, 0.5403 mmol) in THF (10 mL) and H_2O (0.200 mL, 11.111 mmol) at room temperature. The mixture was stirred for 24 h at room temperature. The reaction was quenched with saturated NH_4Cl. HCl (12 M, 4 mL) in MeOH (20 mL) was added. The resulting mixture was stirred for 48 h at room temperature. The reaction was quenched with saturated $NaHCO_3$ and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash chromatography by using 15% EtOAc in hexane to afford indicol (**1**) (0.3868 g, 98%) as a white solid. R_f: 0.40 (20% EtOAc in hexane); m.p. 63–65°C; $[\alpha]_D^{20} = -43.5$ ($c = 1.50$ in $CHCl_3$), lit:[14] $[\alpha]_D^{20} = -44.0$ ($c = 0.426$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.84$ (s, 1H), 4.67 (s, 1H), 2.75 (s, 1H), 2.65–2.57 (m, 2H), 2.53–2.31 (m, 2H), 2.35 (td, $J = 13.2$, 4.9 Hz, 1H), 2.13–2.10 (m, 1H), 1.95–1.90 (m, 1H), 1.87 (d, $J = 13.3$ Hz, 1H), 1.81–1.52 (m, 7H), 1.39 (dd, $J = 14.3$, 6.1 Hz, 1H), 1.11 (d, $J = 6.9$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H), 1.03–0.97 (m, 1H), 1.00 (s, 3H), 0.71 ppm (s, 3H); IR (CH_2Cl_2): $\tilde{\nu} = 3585$ (O−H), 2971, 2943, 1708 (C=O), 1647 cm^{-1} (C=C); LRMS (EI): m/z: 320 $[M]^+$ (3), 302 (4), 292 (4), 277 (5), 259 (6), 248 (3), 247 (9), 235 (12), 229 (37), 221 (39), 203 (11); HRMS (EI): m/z: calcd for $C_{20}H_{32}O_3$: 320.2351; found: 320.2350.

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