A "Chiral Aldehyde" Equivalent as a Building Block Towards Biologically Active Targets

Barry M. Trost* and Matthew L. Crawley[a]

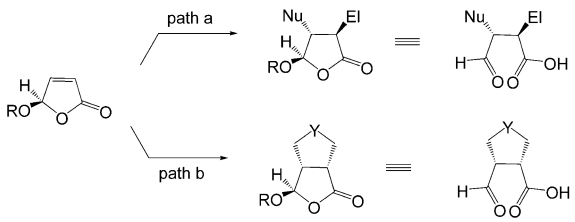
Abstract: Chiral γ-aryloxybutenolides, readily accessible through dynamic kinetic asymmetric transformation (DYKAT) of racemic acyloxybutenolides, were utilized as "chiral aldehyde" building blocks for intermolecular cycloadditions and Michael reactions. Unprecedented selectivity in trimethylenemethane cycloadditions with this building block allowed an efficient synthesis of a novel metabotropic glutamate receptor 1 antagonist in development by the Bayer corporation. These studies further inspired work that culminated in the total synthesis of (+)-brefeldin A, a natural product with a range of significant biological properties. All of the stereochemistry in this target molecule was derived from two palladium-catalyzed asymmetric allylic alkylation reactions. The *trans*-alkenes were synthesized by a Julia olefination and a ruthenium-catalyzed *trans*-hydrosilylation-protodesilylation protocol. The route to (+)-brefeldin A lends itself to analogue syntheses and was completed in 18 steps in 6% overall yield.

Keywords: alkylation · asymmetric synthesis · brefeldin A · chiral butenolides · total synthesis

Introduction

The art and genius of synthetic organic chemistry is often best expressed in the enantioselective total synthesis of biologically significant molecules. In this regard, "chiral aldehyde" building blocks offer enormous potential in allowing access to synthetic targets.[1] Previously, allylic acetals derived from chiral diols and enals have been used in a number of cases to direct stereocontrolled reactions, including cuprate additions, cyclopropanations, and additions of electrophiles to the adjacent olefin.[2] While a variety of approaches for setting stereogenic centers have been established, development of catalytic enantioselective methods to achieve this goal has been a challenging undertaking.[3] The ability to design a synthetic strategy without the restrictions of starting materials from a chiral pool or of the cost and often poor availability of chiral auxiliaries has differentiated syntheses using asymmetric catalytic processes from other approaches.[4a] The use of "chiral aldehyde" building blocks derived from asymmetric allylic alkylation (AAA) reactions for stereospecific reaction of double bonds provides a unique opportunity to access complex molecules with multiple stereogenic centers.[4b]

One such building block, γ-hydroxybutenolide derivatives, serve as particularly useful ones. To the extent that the stereochemistry of C-4 can be propagated by directing either stepwise [Eq. (1), path a] or concerted [Eq. (1), path b] processes, the resulting adducts are functionally equivalent to a vicinal aldehyde–carboxylic acid existing in a protected form. The potential value of such a building block led to an elegant series of studies by Feringa et al.[5] In the first iteration, a chiral auxiliary approach with menthol provided a diastereomerically pure γ-menthoxybutenolide.[5a] A more appealing strategy effected an enantioselective enzymatic acylation to form a γ-acetoxybutenolide.[5b] However, as the authors subsequently note, "the high sensitivity of the 5-acyl substituent in subsequent C–C bond formation is an important incentive for the alkoxy furanone."[5c]



(1)

The development of dynamic kinetic asymmetric transformations (DYKATs) in AAA reactions, through which race-

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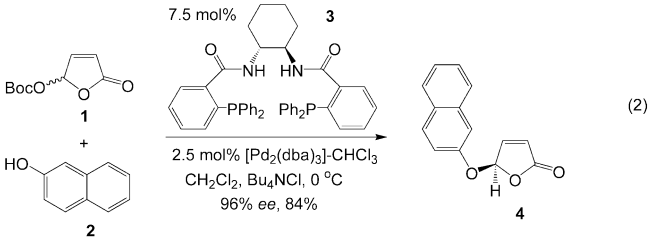
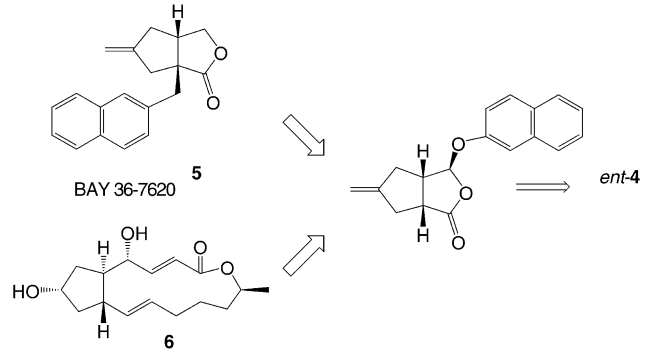
mic material can be completely converted into enantiopure adducts through interconversion of diastereomeric π-allyl intermediates, has significantly expanded the scope and utility of the AAA process.[6] DYKATs offer a significant advantage over the traditional kinetic resolutions in terms of yield and the avoidance of costly chiral auxiliary reagents. Entry into chiral γ-aryloxybutenolides was achieved by employment of a palladium-catalyzed AAA in a DYKAT with racemic butenolide **1**, (*R*,*R*)-ligand **3**, tetrabutylammonium chloride, and 2-naphthol (**2**) as the nucleophile to afford adduct **4** in 84% yield and 96% *ee* [Eq. (2)]. This approach pro-



(2)

vides access to either enantiomer in high *ee* simply by switching the ligand and yields a derivative that is quite suitable for subsequent C–C bond-forming events.

In this paper we explore the utility of this readily available chiral building block for subsequent C–C bond-forming reactions. Special attention was given to cycloadditions, most notably 1,3-dipolar cycloadditions including that of trimethylenemethane. Indeed, very simple strategies emerge for the syntheses of the metabotropic glutamate receptor antagonist represented by BAY 36-7620 and the fungal metabolite (+)-brefeldin A, which, among its myriad biological functions, disrupts the Golgi complex and induces apoptosis (see Scheme 1).

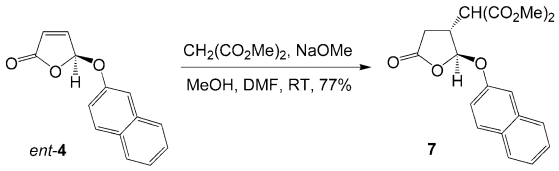


Scheme 1. Retrosynthetic analysis of BAY 36–7620 and (+)-brefeldin A.

The biological significance of (+)-brefeldin A (**6**) has been heavily studied. The unique mode of action in a variety of therapeutic areas combined with the potential for analogues makes it a particularly attractive synthetic target.[7] The five stereogenic centers and the two *trans*-olefins in the bicyclic macrolactone arrangement provide a range of opportunities and a host of challenges. The numerous synthetic efforts emphasize this point. Despite the fact that the first enantioselective total synthesis of (+)-brefeldin A (**6**) was completed over two decades ago,[8] most of the efforts since have either required a strategy with over 20 steps for the longest linear sequence or have been completed with under 2% overall yield.[9,10] Among the shortest syntheses are those of Corey,[9e] Haynes,[9m] Suh,[9p] Romo,[9s] and Kobayashi.[9k]

Results

Michael additions to 2-(2-naphthoxy)-5-oxo-2,5-dihydrofuran: A large variety of substituents, including ethers, amines, and alkyl groups, have been stereoselectively introduced through Michael additions of stabilized nucleophiles.[11] In order to establish benchmark comparisons with other systems, nucleophiles known to add to γ-substituted butenolides with facial selectivity were examined. A good example was the addition of dimethyl malonate to *ent*-**4** [Eq. (3)].



(3)

This conjugate addition afforded butyrolactone **7** in 77% yield as a single diastereomer, comparable to the reported addition of dimethyl malonate to (*R*)-(−)-5-[(1*R*,2*S*,5*R*)-menthyloxy]-2(5*H*)-furanone (**8**).[12]

The *trans* configuration of lactone **7** was assigned, in part, on the basis of comparisons with Feringa's systems and, in part, from macromodel calculations of the minimum-energy conformation of the *trans* product **6**, by means of an extensive conformation search (5000 iterations) with an MM2 force-field in solution phase with chloroform as solvent (Figure 1). The minimized conformation displayed a dihe-

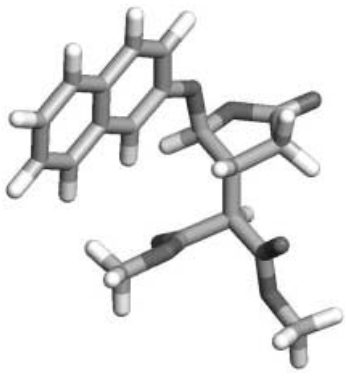
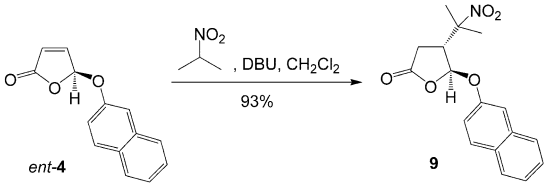


Figure 1. Macromodel-predicted minimum-energy conformation of lactone **7**.

dral angle of 82.1° that was consistent with the small coupling constant of 2.4 Hz observed between the β- and γ-protons of the lactone. Other low-energy conformations within

0.2 kcal mol^{-1} of the predicted ground state had similar dihedral angles (80.2–83.5°) between the adjacent protons. The *syn* conformation of adduct **7** had a dihedral angle of 22° that was inconsistent with the observed small coupling constant. Further details of the stereochemical assignments for lactone **7** and other Michael addition adducts are discussed later in this section.

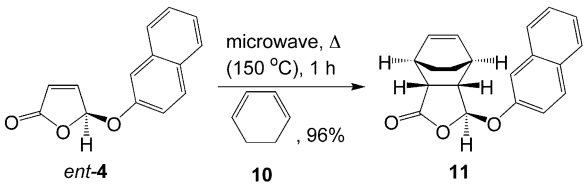
Since preliminary investigations indicated that aryloxybutenolide **4** could function in Michael additions as well as or better than other chiral butenolides, we decided to investigate whether other stabilized nucleophiles not previously investigated for the other butenolides would add selectively. The addition of nitroalkanes was an evident choice. Treatment of 2-nitropropane with butenolide *ent*-**4** in the presence of one equivalent of DBU afforded lactone **9** in 93% yield as a single diastereomer [Eq. (4)]. As in the case of the malonate, the 2.9 Hz coupling of the vicinal hydrogens is in accord with the depicted *trans* geometry.



(4)

Diastereoselective cycloaddition reactions with the butenolide: Diels–Alder reactions of both cyclic and acyclic dienes with 5-menthyloxy-2(5*H*)-furanone have been well documented by Feringa and co-workers.[13] The diastereoselectivities were outstanding in most of the reported examples, though the yields were sometimes moderate (44 to 77%). To benchmark chiral butenolide **4**, two Diels–Alder reactions were examined.

The first cycloaddition was with 1,3-cyclohexadiene **10** and butenolide *ent*-**4** [Eq. (5)]. The reaction was carried out



(5)

neat in a microwave and gave quantitative conversion (96% yield after silica-gel chromatography) into a single diastereomer **11**. The stereochemistry of *endo*-adduct **11** was assigned by analogy from Feringa's[12] examples and by evaluation of the coupling constants of the γ- and β-protons in comparison with a macromodel MM2 force-field solution-phase minimum-energy structure (Figure 2). The lactone γ-proton displayed a doublet at $\delta = 5.70$ ppm, with a coupling constant of 1.7 Hz consistent with the dihedral angle of 104° predicted by the modeling calculations. This was in agreement with the coupling constant of 1.5 Hz observed by Feringa for the γ-lactone proton in the menthyloxy adduct.

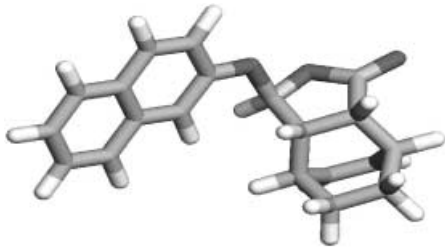
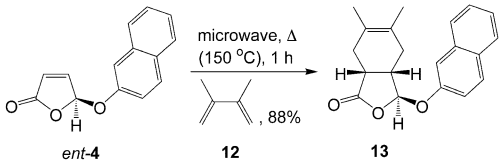


Figure 2. Energy-minimized structure of Diels–Alder adduct **11**.

The Diels–Alder reaction between 2,3-dimethylbutadiene **12** and butenolide *ent*-**4** afforded *anti* cycloadduct **13** as a 95:5 diastereomeric mixture of the *anti* and *syn* adducts [Eq. (6)]. The ratio was assigned by ^{1}H NMR spectroscopy,

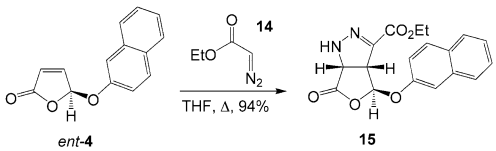


(6)

by comparison of the integration of the γ-lactone proton signals ($\delta = 5.79$ ppm singlet for *anti* vs $\delta = 6.08$ ppm doublet, $J = 2.2$ Hz for *syn*). The observation of no coupling constant between the β- and γ-protons for adduct **13** was consistent with Feringa's Diels–Alder adduct for the menthyloxy system. In that case Feringa confirmed the relative stereochemistry through X-ray crystallography.

Since the [4+2] cycloaddition reactions proceeded with excellent selectivities and yields, the next logical step was to examine [3+2] dipolar cycloaddition reactions. It was desirable to ascertain whether butenolide **4** could provide results equally impressive as observed in other butenolide systems for these reactions, and also to see whether previously untried cycloaddition reactions with butenolides could proceed diastereoselectively.

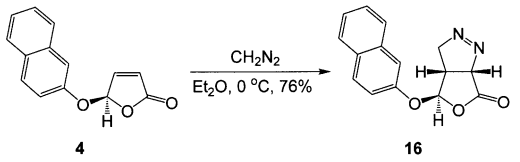
One straightforward comparison was pursued in the cycloaddition between ethyl diazoacetate **14** and butenolide *ent*-**4** to give cycloadduct **15** as a single diastereomer in 94% yield [Eq. (7)]. The assignment of stereochemistry was possible



(7)

by comparison to the known menthyloxy adduct described by Feringa,[14] who obtained the adduct in 65% yield and in an *anti*/*syn* ratio of 91:9. The *anti* adduct had no coupling between the β- and γ-protons, while the *syn* adduct had a 7.0 Hz coupling constant. In the case of adduct **15**, the γ-proton displayed a singlet at $\delta = 6.49$ ppm. This chiral butenolide *ent*-**4** demonstrated both improved yield and selectivity in this cycloaddition reaction.

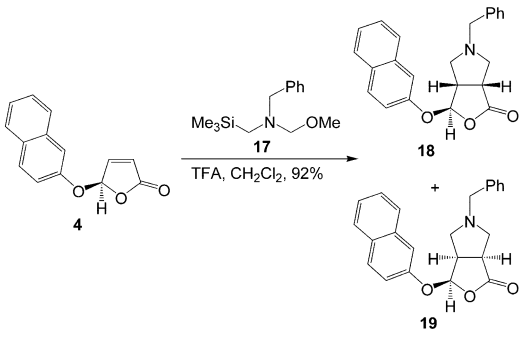
Cycloaddition reactions with diazomethane in ethereal solution at various temperatures with or without additives gave a crude diastereoselectivity of 4:1, to afford pyrazoline **16** in 76% yield and as a single diastereomer after chromatography [Eq. (8)]. The corresponding reaction of the men-



(8)

thoxy acceptor is reported to provide a selectivity of 3:1 in 55% yield.[15] The stereochemistry of addition was assigned by comparison to similar systems and by use of the Karplus relationship, which indicates that the coupling constant between the protons should be less than 2.0 Hz for the *anti* addition product while the *syn* addition product should have a coupling constant between 8.0 and 11.0 Hz. The observed signal for the γ-lactone proton of the major cycloadduct **16** at $\delta = 5.77$ ppm appeared as a doublet, $J = 1.5$ Hz, consistent with the assigned stereochemistry.

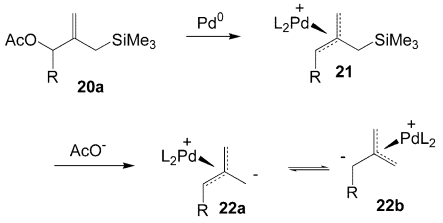
Access to 3,4-*cis*-bis-functionalized pyrrolidines is possible through diastereoselective addition of azomethine ylides to chiral butenolides. Successful studies on this type of cycloaddition under ultrasonic conditions have been reported. Treatment of butenolide **4** with azomethine precursor **17** afforded pyrrolidine derivatives **18** and **19** in 92% combined yield, as a 3.5:1.0 mixture of diastereomers [Eq. (9)]. The di-



(9)

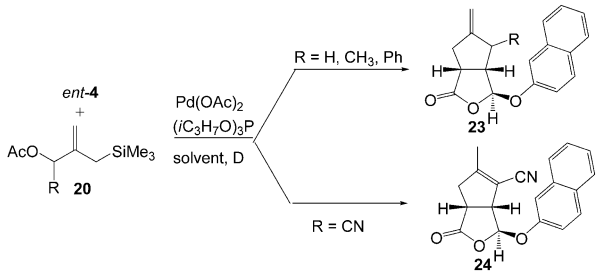
astereomers were separable by silica-gel chromatography and readily identified, as in the previous cases, by examination of the coupling constants between the γ- and β-lactone protons. For the major *trans* adduct **18**, the γ-proton displayed a signal at $\delta = 5.92$ ppm as a doublet, $J = 1.5$ Hz, while the in *syn* adduct **19** the γ-proton displayed a signal at $\delta = 6.21$ ppm as a doublet, $J = 6.6$ Hz.

The success with classical [4+2] and [3+2] cycloaddition reactions inspired the examination of trimethylenemethane (TMM) cycloaddition reactions with butenolide **4**. The acetate **20** was available in three steps and 48% yield by methods previously developed in these laboratories starting from 2-methyl-2-propen-1-ol.[16] The TMM precursor **20** generates a dipole in situ after treatment with palladium(0), to form palladium π-allyl intermediate **21**. The α-silyl group subsequently undergoes desilylation, presumably by attack of the acetate anion on silicon, to give dipole **22** [Eq. (10)].[17] Dipole **22** can then add to electron-deficient olefins.



(10)

Treatment of acetate **20a** with butenolide *ent*-**4** in the presence of palladium(II) acetate with triisopropyl phosphite as ligand in toluene at reflux afforded cyclopentanoid adduct **23a** in 93% yield and as a single diastereomer [Eq. (11)]. Lactone **23a** was a white solid stable to storage



(11)

a) R = H; b) R = CN; c) R = OAc; d) R = Me; e) R = Ph

at ambient temperature without the need for inert atmosphere.

The stereochemistry of addition was assigned as *trans* by comparison of the macromodel-generated minimum-energy conformations of the *trans* and *cis* adducts (MM2 force-field with chloroform as solvent) with the observed coupling constants for lactone **23a** (Figure 3). The predicted dihedral

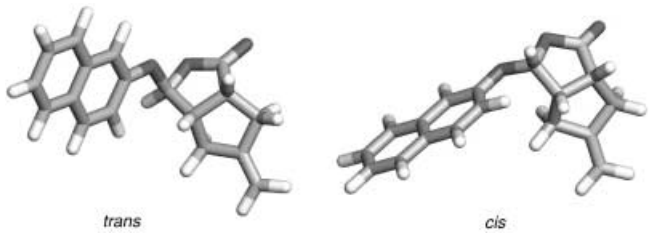


Figure 3. Conformations of the *trans* and *cis* TMM adducts **23a** predicted by Macromodel.

angle between the β- and γ-protons on the lactone was 92° for the *trans* adduct and 23° for the *cis* adduct. The observed signal for the γ-proton was a singlet at $\delta = 5.90$ ppm, consistent with the *trans* geometry.

The success with the unsubstituted TMM cycloaddition prompted an investigation of the reactions of substituted TMM dipoles **20a–e** with the butenolide. These substituted TMM precursors were synthesized by previously described methods,[18] and the butenolide was then subjected to the usual Pd^0 catalyst system for such cycloadditions to provide adducts **23a–e** (Table 1). The solvent effect on the facial selectivity is noteworthy; that is, a higher diastereoselectivity was observed in toluene than in THF even though the former is at considerably higher temperature (Table 1, entries 3 and 4).

Table 1. TMM cycloadditions to butenolide *ent*-**4**.[a]

Entry	Substrate	Conditions	Product	Yield [%]	*dr* (epimers)[b]
1	**20a**	toluene, 100 °C, 12 h	**23a**	93	>98:2
2	**20a**	THF, 65 °C, 24 h	**23a**	93	>98:2
3	**20b**	THF, 65 °C, 12 h	**24**	94	5.5:1
4	**20b**	toluene, 100 °C, 12 h	**24**	91	94:6
5	**20c**	toluene, 100 °C, 12 h	–	–	–
6	**20d**	toluene, 100 °C, 48 h	**23d**	60	>98:2 (1:1)
7	**20e**	toluene, 100 °C, 24 h	**23e**	79	>98:2 (4:1)

[a] All reactions were run as summarized in Equation (11). [b] Diastereomeric ratios are of the crude reaction mixture.

Thus, with the unsubstituted TMM–PdL_2 species, reaction proceeds via complex **22b** and not **22a**. Diacetate **20c** did not react under the reaction conditions, and gave recovered starting material (Table 1, entry 5). In the case of the cyano-substituted TMM reaction (Table 1, entries 3 and 4), the exocyclic double bond of the initial product isomerized to the endocyclic position under the reaction conditions. While the epimeric ratio with respect to the methyl group in entry 6 was 1:1, the ratio increased to 4:1 in the phenyl-substituted system (Table 1, entry 7).

As in the case of the unfunctionalized TMM adduct **23a**, the γ-protons on the lactones produced singlets (the observed chemical shifts were between $\delta = 5.80$ and 6.20 ppm), consistent with the *trans* rather than the *cis* adducts. The regio- and stereochemistry of addition for the substituent on both epimers of the methyl (**23d$_1$** and **23d$_2$**) and phenyl (**23e$_1$** and **23e$_2$**) derivatives were established by nOe experiments (Figure 4). The methyl-substituted derivatives were readily assigned by observing that, in compound **23d$_1$**, protons H_a and H_b displayed a 2.8% nOe, while there was no nOe between protons H_a and H_c. Conversely, adduct **23d$_2$** showed protons H_a and H_b with no nOe, while protons H_a and H_c displayed a 3.0% nOe.

In the case of phenyl adducts **23e$_1$** and **23e$_2$**, isolated in a 4:1 ratio, the same type of observations allowed the relative stereochemistry to be assigned. In compound **23e$_1$** the protons H_a and H_b displayed a 4.2% nOe, while there was no nOe between protons H_b and H_c. Conversely, adduct **23e$_2$** showed no nOe between protons H_a and H_b, while protons H_b and H_c displayed a 7.2% nOe.

Further studies, including the synthesis of the Bayer drug 36-7620 and the total synthesis of (+)-brefeldin A (**5**), further confirmed the *trans* nature of the cycloaddition adduct through the conversion of TMM adducts into known compounds.

A concise synthesis of Bayer compound 5: The unsubstituted TMM adduct **23a** proved to be a versatile building block and provided an opportunity for efficient access to a Bayer drug in development, BAY 36-7620 (**5**). This compound is part of a novel class of metabotropic glutamate receptor 1 antagonists invented by Bayer.[19] It is a specific and potent noncompetitive mGluR1 antagonist, structurally not resembling glutamate, which inhibits >60% of mGluR1 constitutive activity at slightly under 11 nM concentration.[19d]

The synthesis of BAY 36-7620 (**5**) was a straightforward process from cyclopentene **23a** (Scheme 2). Reductive removal of the aryloxy group by use of sodium borohydride under basic conditions, followed by lactonization with aqueous hydrochloric acid, afforded γ-dihydrolactone **25** in 83% yield. Akylation of adduct **25** with 2-bromomethylnaphthalene afforded adduct **5** in 83% yield.

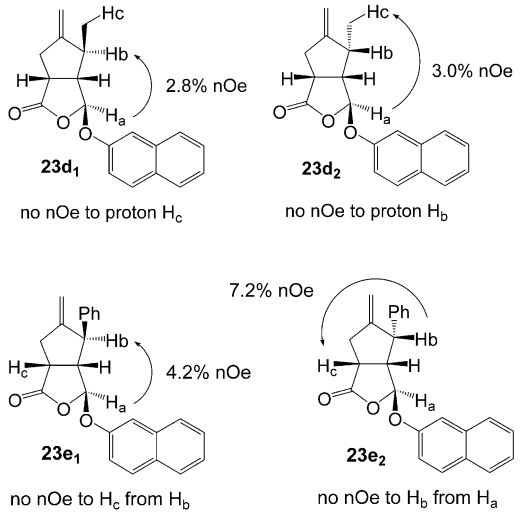
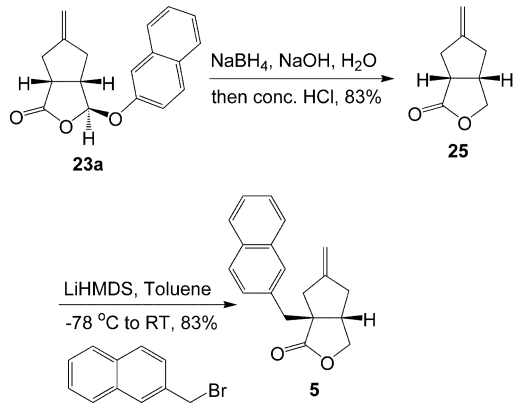


Figure 4. Assignment of relative stereochemistry for cycloadducts **23d** and **23e**.

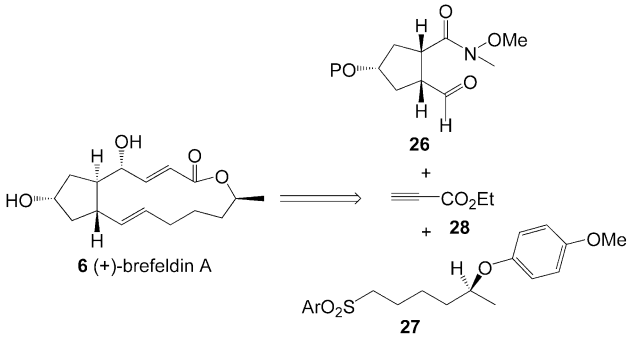


Scheme 2. Synthesis of Bayer drug 36–7620 (**5**).

The ^{1}H NMR data and the sign and magnitude of rotation matched the Bayer data {$[\alpha]_D = -30 \pm 0.1$ ($c = 1.60$ in $CHCl_3$) vs. Bayer data $[\alpha_D] = -33.0$ ($c = 1.0$ in CH_2Cl_2)}. Thus, a concise, six-step synthesis of Bayer 36-7620 (**5**) was completed in 44% yield from commercially available furfural, compared to the eight-step and 16% yield process reported by Bayer. The use of this methodology should provide access to both enantiomers of **5** as well as a number of other alkylation derivatives, though only one was prepared.

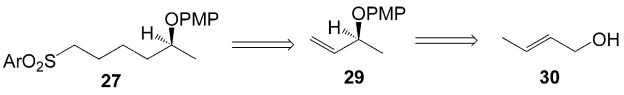
Total synthesis of (+)-brefeldin A (6): There have been many synthetic efforts towards (+)-brefeldin A (**6**) because of its unique structural features. The majority of these approaches have used a convergent synthetic approach disconnecting the molecule into a cyclopentane core fragment and side chains. These routes have closed the macrolide by lactonization, cycloaddition, or metathesis. This strategy appealed to us, though it was important to design a synthesis that could avoid many of the protecting and functional group manipulations involved that have caused previous syntheses to be somewhat lengthy.

We envisioned (+)-brefeldin A (**6**) coming from a core fragment **26**, a six-carbon lower side chain **27**, and ethyl propiolate (**28**) (Scheme 3). The sulfone **27** would be coupled in a modified *trans*-selective Julia olefination[20] with aldehyde **26**. The remaining propiolate fragment would be added by addition to a Weinreb amide, followed by epimerization of the proton α to the carbonyl group. Subsequent deprotection, ester saponification, macrolactonization, and global deprotection would complete the total synthesis of **6**.



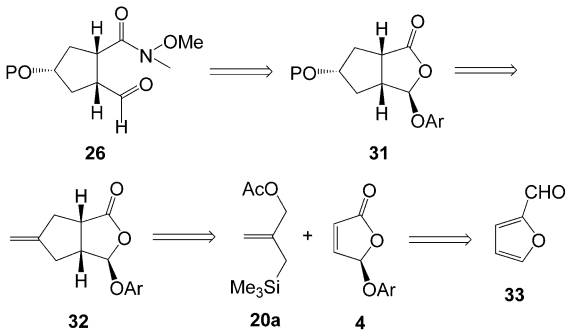
Scheme 3. Retrosynthetic analysis of (+)-brefeldin A (**6**).

The six-carbon lower side chain sulfone **27** would be derived from the chiral four-carbon allylic ether **29**, itself produced from a regio- and enantioselective allylic alkylation of the carbonate of (*E*)-crotyl alcohol (**30**) (Scheme 4). The allylic ether **29** could be transformed into the Julia precursor **27** by any number of two-carbon homologation protocols. The aryl group of sulfone **27** was envisioned as a tetrazole sulfone that has shown exceptional versatility in the one-pot Julia olefination.



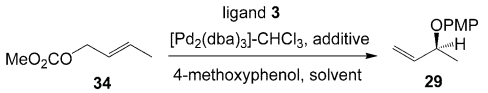
Scheme 4. Retrosynthetic analysis of the lower side chain **27**.

Core aldehyde **26** could be formed from lactone **31** by opening with *N*,O-dimethylhydroxylamine (Scheme 5). The lactone **31** would be synthesized from cyclopentene **32**, itself derived from a diastereoselective [3+2] trimethylenemethane (TMM; generated in situ from allylic acetate **20a**) cycloaddition reaction with chiral butenolide **4**. Butenolide **4** was derived through an AAA reaction in a DYKAT as previously described, originating from furfural **33**.



Scheme 5. Retrosynthetic analysis of the cyclopentane core **26**.

Synthesis of the C(11)–C(16) lower side chain—a first-generation approach: The possibility of using a catalytic enantioselective reaction to set the remote C(15) chiral center of (+)-brefeldin A (**5**) was appealing. In a continuation of the research of Trost and Toste on AAA reactions of allylic carbonates with phenols, methyl crotyl carbonate **34** was alkylated with 4-methoxyphenol under a variety of conditions [Eq. (12), Table 2].[21] The initial results reported by Toste were encouraging, giving 87:13 branched to linear selectivity, though only 60% *ee*. Toste discovered that the enantioselec-



(12)

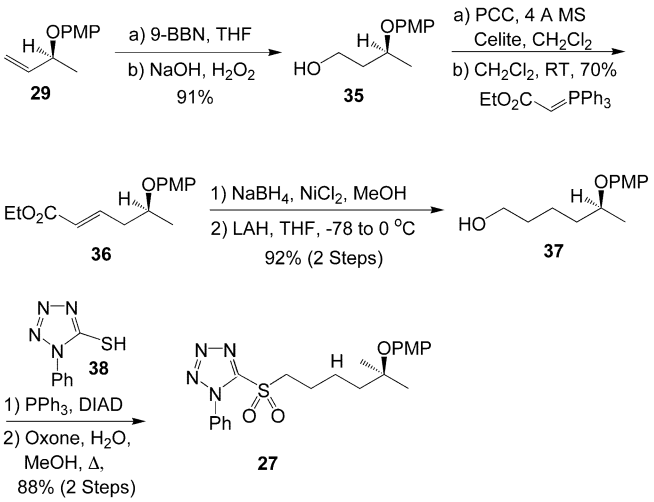
Table 2. Asymmetric allylic alkylation of 4-methoxyphenol with crotyl carbonate.[a]

Entry	Pd_2dba_3 [mol%]	Ligand [mol%]	Conditions	Yield [%]	branched/ linear	% *ee*
1	1.0	3.0	THF, RT, 0.5 M	85	87:13	60
2	1.0	3.0	CH_2Cl_2, 0 °C, 0.5 M	78	92:8	71
3	0.25	0.75	CH_2Cl_2, 0 °C, 0.5 M, 30% Bu_4NCl	86	97:3	31
4	0.25	0.75	CH_2Cl_2, 0 °C, 0.5 M	75	95:5	81
5	0.25	0.75	CH_2Cl_2, 0 °C, 0.5 M, K_2CO_3	75	93:7	81
6	**0.25**	**0.75**	**toluene, 0 °C, 0.1 M**	**95**	**96:4**	**90**
7	0.25	0.75	branched SM, as entry 4	92	96:4	32

[a] All reactions run as summarized in Equation (12).

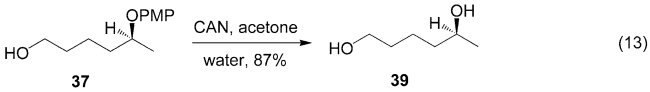
tivity plummeted to 31% with the addition of tetrabutylammonium chloride, suggesting that π–σ–π interconversion was unfavorable for this alkylation. Further investigation revealed that toluene was the optimum solvent for this reaction and that dilute conditions at 0°C are important to maximize the selectivity. This reaction is an example of enantioselection derived from preferential ionization through enantioselective coordination to one of the prochiral olefin faces.[22] The optimized conditions gave yields over 95% with 90% *ee* and 96:4 branched to linear ratio (entry 6, Table 2). This reaction was robust and performable on 10 gram scales with no change in selectivity.

The chiral allylic ether **29** was transformed into enoate **36** by hydroboration–oxidation to alcohol **35** and subsequent one-pot oxidation to the aldehyde and an in situ Wittig reaction in an overall yield of 64% (Scheme 6). Only one chromatographic separation was necessary in this sequence, after the final step. Enoate **36** was transformed in a sodium borohydride 1,4-reduction catalyzed by nickel dichloride[23] followed by reduction with lithium aluminium hydride to afford the saturated alcohol **37** in 92% yield over two steps. The primary alcohol **37** was readily converted into sulfone **27** in 88% yield by Mitsunobu coupling of 1-phenyl-5-thioltetrazole (**38**) followed by oxone oxidation.[24] The total sequence afforded sulfone **27** in six steps and 52% yield from **29**.



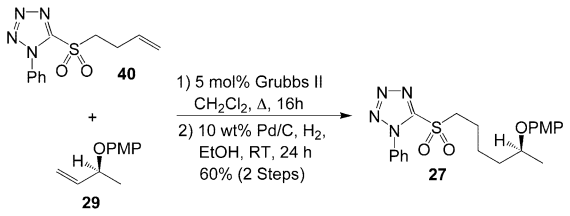
Scheme 6. Completion of the C(11)–C(16) lower side chain fragment **27**.

The absolute stereochemistry of the adduct **35** derived from the AAA reaction with crotyl carbonate was established by conversion of intermediate **37** into **39** by use of cerium ammonium nitrate in acetone/water to afford diol **39** in 87% yield [Eq. (13)]. Diol **39** is known, and its spectral data as well as the sign and magnitude of its optical rotation ($[\alpha]_D = +6.6 \pm 0.3$ ($c = 0.70$ in CH_3OH)) agree well with the reported values ($[\alpha]_D = +7.0 \pm 2.0$ ($c = 0.89$ in CH_3OH)).[25] This unambiguously established that no epimerization had occurred in the transformation to intermediate **37** and confirmed the results from the AAA reaction.



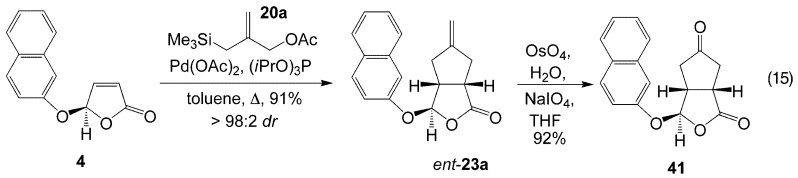
(13)

An alternative approach to the lower side chain: While the initial route to sulfone **27** gave a high overall yield, it was also somewhat lengthy. Several other ways to make the lower side chain **27** were examined, including conversion of allylic ether **29** into an alkyl iodide (by hydrozirconation-iodination of **28**) as an alkylation partner. Unfortunately these efforts were unsuccessful. A revised approach utilized a cross-metathesis reaction between allylic ether **29** and two equivalents of sulfone **40** [Eq. (14)]. The latter compound was prepared in 86% overall yield through a Mitsunobu reaction between a tetrazolethiol and homoallyl alcohol with subsequent ammonium molybdate oxidation. Hydrogenation of the olefin with palladium on carbon cleanly afforded sulfone **27** in two steps and 60% yield. This route reduces the number of linear steps from **29** to only two.



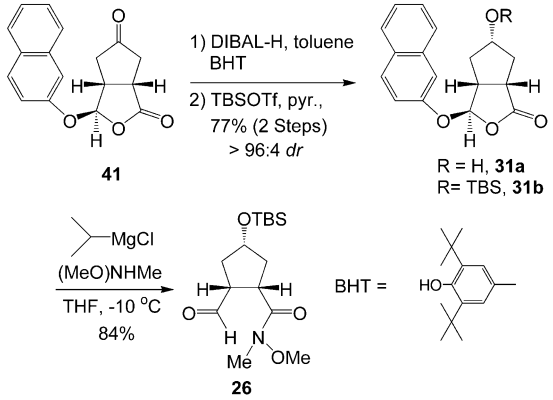
(14)

Synthesis of the core—a first-generation approach: The “chiral aldehyde” equivalent **4** was utilized as the key building block for the core synthesis of (+)-brefeldin A (**6**). The previously described cyclopentene **23a** was oxidatively cleaved in a one-pot protocol with catalytic osmium tetroxide and sodium periodate[26] to give a 92% yield of ketone **41** [Eq. (15)]. The crude adduct was sufficiently pure for use in subsequent transformations without further purification.

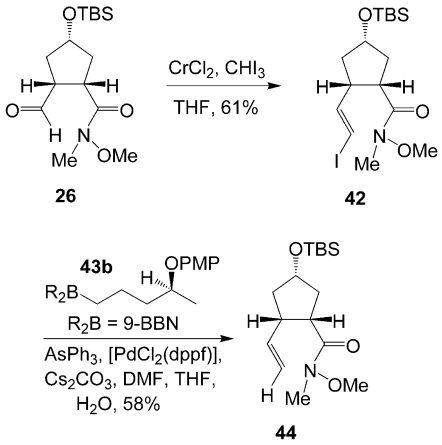


(15)

Ketone **41** was chemo- and diastereoselectively reduced (96:4 dr) to alcohol **31a** by Yamamoto’s method[27] (Scheme 7). It should be noted that the transformation was not as trivial as initially expected and that a variety of reducing agents including sodium borohydride, diisobutylaluminium hydride, and lithium aluminium hydride led to preferential reduction of the lactone instead of the ketone. Other reduction methods led either to the wrong chemoselectivity or to no diastereoselectivity. Without purification,



Scheme 7. First-generation synthesis of the core **26**.



Scheme 8. Further efforts towards the cyclopentane core.

the alcohol **31a** was silyl-protected to afford intermediate **31b** in 77% yield for the two steps. By a modification of a Merck protocol, in which twice the normal amounts of base and amine were utilized,[28] the lactone **31b** was then opened to amide/aldehyde **26** in 84% yield with isopropylmagnesium chloride as base. This completed the eight-step sequence from furfural in 38% overall yield.

To validate the presumed stereochemistry of intermediate **26**, nOe experiments were conducted. The results confirmed the predictions. The proton H_a displayed nOes of equal magnitudes of 3.0% to both H_b and H_c (Figure 5). This verified that the three protons were in *cis* positions and that no epimerization had occurred during the opening of the lactone.

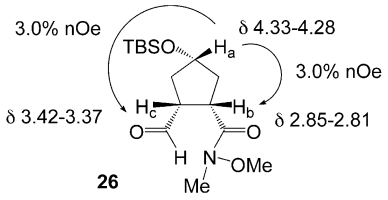
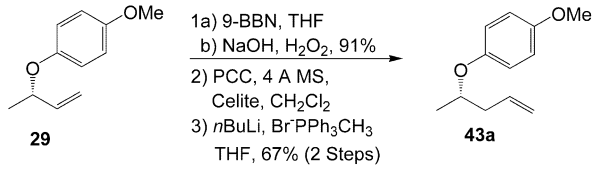


Figure 5. Confirmation of the relative stereochemistry for aldehyde **26**.

Further elaboration of the core fragment by the planned Julia olefination with sulfone **27** was unsuccessful. Both lithium and potassium hexamethyldisiliazane were utilized as bases in dimethoxyethane, tetrahydrofuran, and toluene as solvents; hexamethylphosphorous amide was also utilized as an additive. Despite a variety of changes, all efforts caused decomposition to a complex mixture.

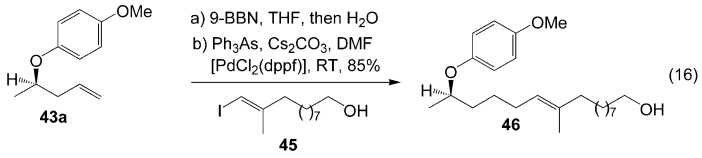
Several explanations for the decomposition were possible. Firstly, the initial adduct of sulfone addition might lactonize. Secondly, the initial aldehyde **26** might epimerize under the basic conditions. Furthermore, the reactivity of the system was probably altered because of the steric demands of the system.

To overcome this obstacle, a modified protocol to attach the lower side chain was devised. Aldehyde **27** was transformed into the *trans*-vinyl iodide **42** in 61% yield by the Takai protocol (Scheme 8).[29] Initial attempts to cross-couple the vinyl iodide **42** under Suzuki conditions[30] with borane derivative **43b** resulted only in the protodeiodination product **44**. The borane **43b** was formed in situ from alkene **43a**. Compound **43a** was derived from chiral allyl ether **29** in three steps and 61% yield (Scheme 9). The formation of

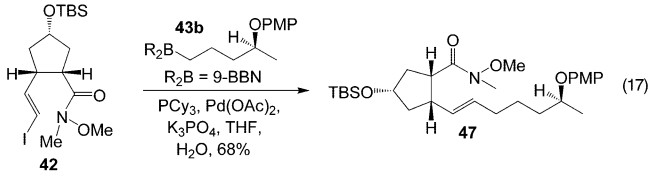


Scheme 9. Synthesis of the C(5) intermediate **43**.

only the undesired **44** was surprising, as the same borane **43b** reacted under identical conditions with the more hindered vinyl iodide substrate **45** to give an 85% yield of *trans*-alkene **46** [Eq. (16)].



However, utilization of the improved cross-coupling protocol under the conditions described by Fu[31] afforded the desired extended core fragment **47** in 68% yield [Eq. (17)]. This intermediate was stable and readily purified by silica-gel chromatography. To confirm that no epimerization had occurred during the Takai reaction or the Suzuki cross-coupling reaction, nOe experiments were conducted on vinyl



iodide **42** and amide **47** (Figure 6). For derivative **42**, proton H_a displayed nOes of equal magnitude of 4.1% to protons H_b and H_c. In the case of amide **47**, proton H_a showed a 2.4% nOe to H_b and 2.2% to H_c. These experiments validated the indicated stereochemistry.

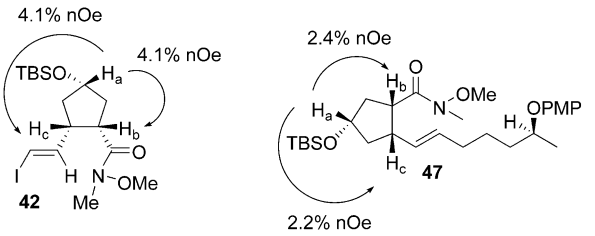
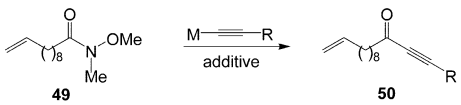


Figure 6. Confirmation of relative stereochemistry for iodide **42** and amide **47**.

Unfortunately, after confirming the stereochemistry and overcoming the obstacles to obtain core **47**, we discovered the material was not suitable for further transformations. The desired addition of ethyl propiolate resulted only in recovered starting material under a variety of conditions. Several dozen sets of reaction conditions were examined, including reductions of the amide and epimerizations of the Weinreb amide α-center. Its lack of reactivity, or under some conditions its decomposition, was quite unexpected.

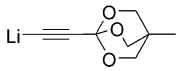
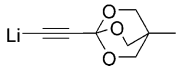
While the lack of reduction was surprising, it was not clear whether Weinreb amides were susceptible to nucleophilic addition of propiolate anions. While numerous examples of addition with the lithium salts of alkyl- and aryl-substituted alkynes are known, there have been no reports of ester-substituted alkynes adding to the amide. Model substrate **49** was selected because of its ease of preparation and was treated with various nucleophiles both in the presence and in the absence of a strong acid catalyst (boron trifluoride etherate) [Eq. (18)]. The results confirmed the reactivity of a Weinreb amide to the conditions under which substrate **47** was inert (Table 3). Notably, the reaction between Weinreb amide **49** and lithium propiolate proceeded at −78 °C in the presence of boron trifluoride etherate.



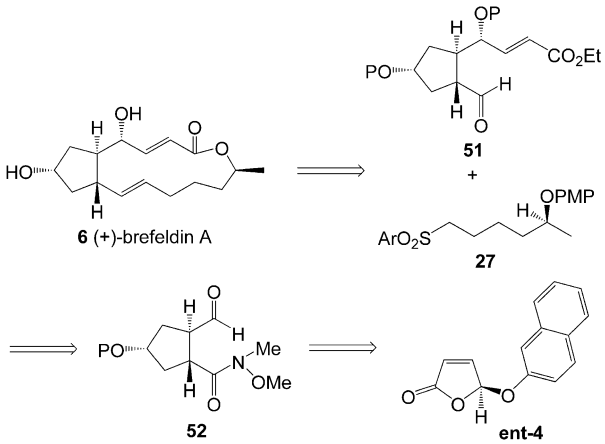
(18)

Synthesis of the core—a second-generation approach: Given this roadblock and the number of difficulties in the original route to (+)-brefeldin A (**6**), a new approach was needed. The flexibility of the butenolide **4** as a “chiral aldehyde” building block is nicely demonstrated by this change of strategy (see Scheme 10). All of the reactivity problems in the first route can be traced to the *cis* configuration of the three cyclopentane substituents. However, despite the *trans*-C(5)–C(9) of the natural product, the initial aldehyde could not be epimerized, because it would give the wrong epimer of the natural product. Instead, if the opposite enantiomer of butenolide **4** was prepared by use of the opposite enantiomer of the ligand in the DYKAT reaction, the aldehyde could then be epimerized and used to install the C(1)–C(3) upper side chain. The amide would be the tether for the C(11)–C(16) fragment. Disconnection of (+)-brefeldin A (**6**) to enoate **51** gives a fragment that could be synthesized from amide **52** by alkyne addition/reduction to the aldehyde, followed by protection and amide reduction. Amide **52** is derived from butenolide *ent*-**4**.

Table 3. Nucleophilic additions to a Weinreb amide.[a]

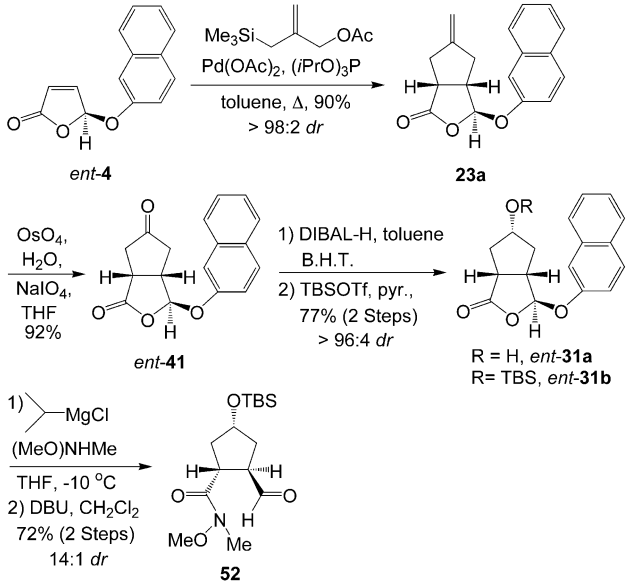
Entry	Nucleophile	Additive	T [°C]/t [h]	Product	Yield [%]
1		–	0/1	**50a**	84
2		$BF_3{\cdot}OEt_2$	−78/0.5	**50a**	78
3	$LiC{\equiv}CCO_2Et$	–	RT/24	starting material	–
4	$LiC{\equiv}CCO_2Et$	$BF_3{\cdot}OEt_2$	−78/1	**50b**	79
5	$BrMgC{\equiv}CH$	–	0/1	**50c**	85
6	$BrMgC{\equiv}CH$	$BF_3{\cdot}OEt_2$	−78/0.5	decomposition	–

[a] All reactions performed in THF as summarized in Equation (18).

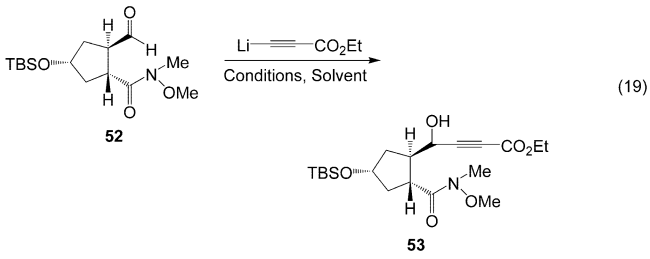


Scheme 10. Revised retrosynthetic analysis.

Efficient synthesis of a functionalized (+)-brefeldin A core: Starting with butenolide *ent*-**4**, the route to core **52** was identical to that in the first core synthesis, with the exception of the epimerization in the last step. Some of the yields differed slightly, but were within 5% of those in the first-generation approach. The final epimerization step proceeded with 14:1 diastereoselectivity to give intermediate **52** (Scheme 11); the undesired isomer could be recycled. The sequence from commercial furfural was completed in nine steps and 32% overall yield and was readily performable on gram scales.



Scheme 11. Second-generation route to the core **52**.



(19)

Table 4. Diastereoselective alkylation of the C(4)-aldehyde.[a]

Entry	Solvent(s)	Conditions	4-(*S*)/4-(*R*)	Yield [%]
1	THF/HMPA 5:1	−78 °C, 4 h	6.0:1.0	88
2	THF/HMPA 9:1	−78 °C, 4 h	4.5:1.0	84
3	THF	−78 °C, 4 h	1.0:3.0	86
4	THF	−78 °C, 4 h, $MgBr_2$	1.0:3.5	80
5	DME	−78 °C, 2 h	1.0:5.0	92
6	DME	−78 °C, 2 h, $MgBr_2$	1.0:6.0	91

[a] Reaction as depicted in Equation (19).

The relative stereochemistry of aldehyde *ent*-**28**, the all-*cis* precursor to aldehyde **52**, had previously been established by nOe studies. Aldehydes **52** and *ent*-**27** had the same molecular weight and connectivity as determined by HRMS, and ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR spectra were virtually identical, the chemical shifts differing by less than 0.1 ppm, with the exceptions of those of the two protons α to the carbonyl groups. Two nOe experiments showed a 2.7% nOe between H_a and H_b and no nOe between H_a and H_c. This confirmed the assumption that the aldehyde **52** had the desired stereochemistry (Figure 7).

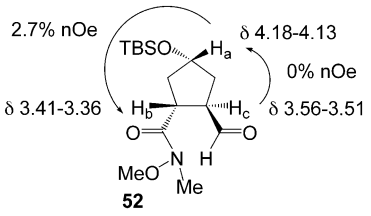
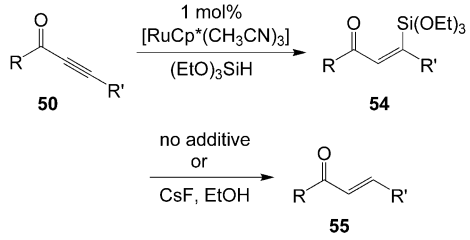


Figure 7. Confirmation of relative stereochemistry for amide **52**.

The introduction of the upper side chain envisioned the use of a new protocol for the formation of *trans*-alkenes from alkynes. To obtain the requisite propargyl alcohol **53**, diastereoselective addition of ethyl propiolate to aldehyde **52** was examined [Eq. (19) ,Table 4]. Variation of conditions allowed access to both epimers at C(4).

Addition of the lithium anion of ethyl propiolate to the core **52** in a THF/HMPA (5:1) solvent mixture at −78 °C (entry 1) afforded the desired alcohol **53** with 6:1 diastereoselectivity. A change in conditions to dimethoxyethane as solvent with use of stoichiometric magnesium bromide afforded the opposite epimer of alcohol **53**. Tentative assignment of the 4*S* stereochemistry as the major adduct for entries 1 and 2 was explained in terms of Felkin–Anh control. The rationale for entries 3–6, Table 4, were explained in terms of chelate control with the best diastereoselectivity being obtained with the better chelating Mg^{2+}.

While the recently reported ruthenium-catalyzed *trans*-hydrosilylation conditions had been reported on a variety of substrates, highly oxygenated substrates had not been examined.[32] Several model compounds were subjected to the reported conditions (Scheme 12, Table 5). Treatment of substrate **50a** afforded adduct **54a** in 92% yield as a 4:1 mixture of regioisomers favoring the β-silyl-substituted product ($\delta = 7.10$ ppm minor vs $\delta = 6.08$ ppm major for the olefin protons). Substrate **50b** did not afford adduct **54b**, but instead directly formed alkene **55b** in 70% yield under the re-



Scheme 12. Model studies for the hydrosilylation protocol.

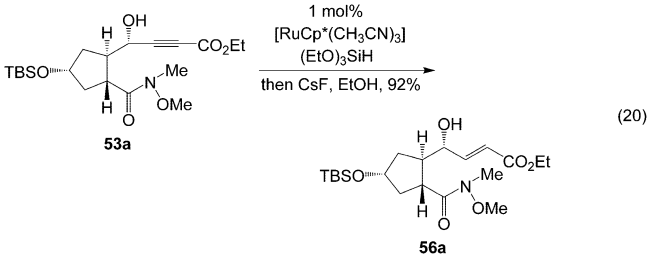
Table 5. Model studies for the hydrosilylation protocol.[a]

Entry	R	R′	Reactant	Comments	Yield [%] (Product)
1	$CH_2CH(CH_2)_8$	$C(OCH_2)_3CMe$	**50a**	no additive	92 (**54a**)
2	$CH_2CH(CH_2)_8$	CO_2Et	**50b**	no additive	70 (**55b**)
3	EtO	$CH(OH)CH_2CH_3$	**50d**	1.5 equiv CsF	77 (**55d**)
4	EtO	$CH(OH)CH(CH_3)_2$	**50e**	1.5 equiv CsF	96 (**55e**)

[a] Reaction depicted in Scheme 12.

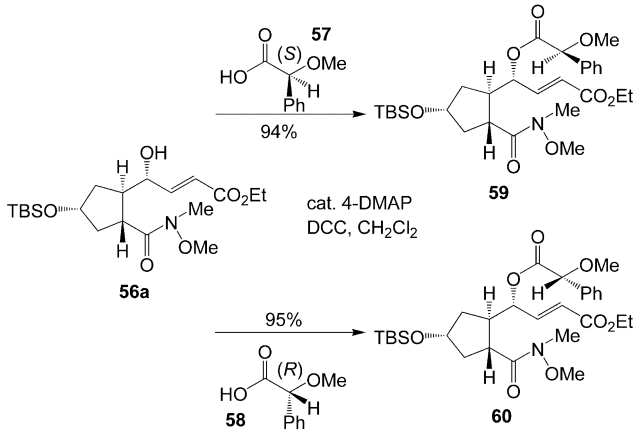
action conditions. Substrates **50d** and **50e**, which approximate alkyne **53a** in their substitution patterns (Table 5, entries 3 and 4), gave 77% and 96% yields of products **55d** and **55e**, respectively, when cesium fluoride in ethanol was added after the hydrosilylation. Thus, ynoates with γ-keto substitution protodesilylate directly, whereas those with γ-alkoxy substitution allow for isolation of the β-vinylsilanes.

The presumed (4*S*)-configured alkyne **53a** was subjected to the same ruthenium-catalyzed conditions. The crude mixture was treated with cesium fluoride in ethanol to afford alkene **56a** in 92% yield [Eq. (20)].



(20)

Derivative **56a** gave an opportunity for confirmation of the absolute stereochemistry of addition of the ethyl propiolate. Coupling of **56a** with (*S*)-*O*-methylmandelic acid (**57**) and (*R*)-*O*-methylmandelic acid (**58**) by a method to determine absolute stereochemistry developed in these laboratories[33] gave derivatives **59** and **60** in 94–95% yield (Scheme 13). The highlighted segments of each ^{1}H NMR spectra (Figure 8) illustrate the profound difference in chemical shift exhibited by the olefin protons between the two compounds.



Scheme 13. Establishment of the relative stereochemistry of the C_4 stereogenic center.

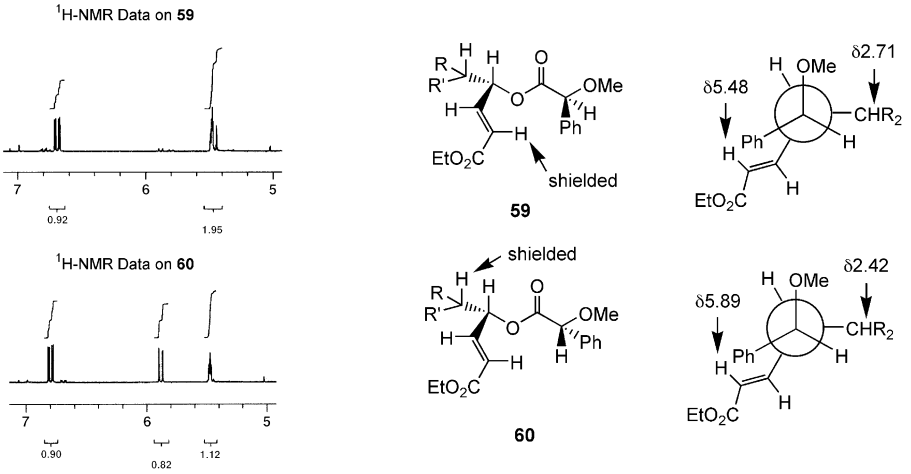
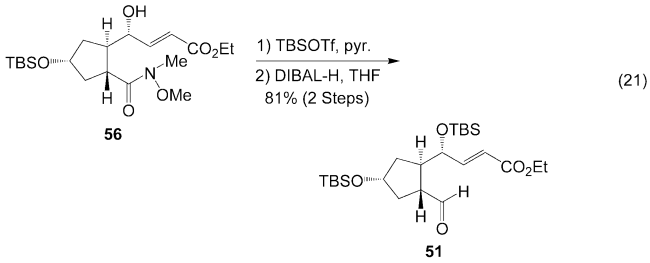


Figure 8. Assignment of stereochemistry through compounds **59** and **60**.

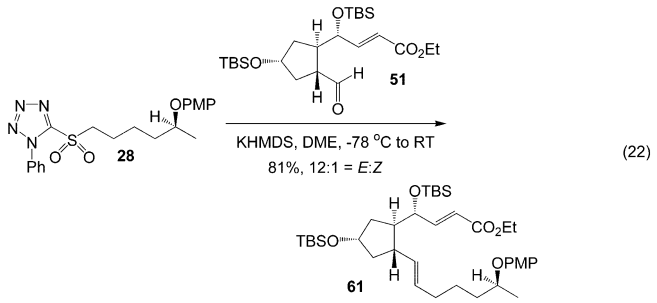
Chemical shift differences between the two spectra fit the pattern established earlier for the methylmandelate derivatives. Shielding of the α-proton of the olefin in the case of **59** versus **60** indicated a difference of 0.4 ppm. A similar magnitude but opposite chemical shift difference was observed for the cyclopentane methine proton, whereby a difference of 0.3 ppm was observed for **59** versus **60** ($\delta = 2.71$ vs 2.42 ppm). This showed shielding of the protons in **60** (Figure 8). These variations are readily explained by the model and confirmed the major adduct was correctly assigned as 4*S*.

After protection of the free alcohol **56** as the *tert*-butyldimethylsilyl ether, the amide was chemoselectively reduced to aldehyde **51** in the presence of the enoate, by use of DIBAL-H as the reducing agent at −78°C [Eq. (21)]. This completed the synthesis of the highly functionalized cyclopentane core in 13 steps and 18% yield from furfural **33**.



(21)

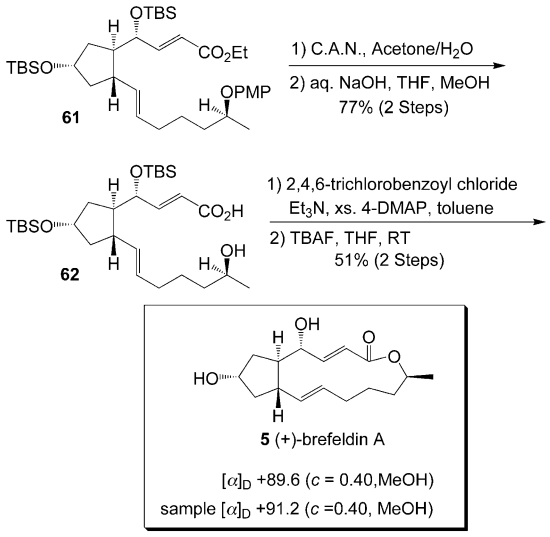
Completion of the total synthesis: With key aldehyde **61** and sulfone **28** in hand, the critical Julia olefination was examined. The optimum conditions involved use of potassium hexamethyldisilazide as the base instead of lithium or sodium hexamethyldisilazide in dimethoxyethane solvent at −78°C. This gave a 12:1 *E*/*Z* selectivity for the formation of alkene **61** [Eq. (22)]. Use of THF as solvent gave a significantly reduced yield (35 vs 81%). This coupling did not have any of the problems encountered in the first-generation synthesis. The *E*/*Z* ratio was assigned by proton NMR



(22)

spectroscopy by comparison of the integration of the major and minor olefin signals. Both the major and minor adducts had olefins with irregular splitting patterns and coupling constants: ($\delta = 5.38$–5.35 and 5.49–5.40 ppm, respectively). The major adduct was presumed to be the *E* adduct, as later confirmed by completion of the total synthesis.

The total synthesis was completed in a four-step sequence. The 4-methoxyphenol group of **61** was oxidatively cleaved by use of cerium ammonium nitrate, followed by ester saponification with sodium hydroxide to afford acid **62** in 76% yield over two steps (Scheme 14). Macrolactonization by Yamaguchi's method[34] to give the bis(silyl)-protected brefeldin **63** and subsequent global deprotection with tetrabutylammonium fluoride afforded (+)-brefeldin A (**6**) in two steps and 51% yield. All of the spectral data, as well as the sign and magnitude of rotation ($[\alpha]_D = +89.6 \pm 0.5$ ($c = 0.40$ in MeOH)), matched those of an authentic sample ($[\alpha]_D = +91.2 \pm 0.4$ ($c = 0.50$ in MeOH))[35] of (+)-brefeldin A (**6**).



Scheme 14. Completion of the total synthesis of (+)-brefeldin A (**6**).

Conclusion

The enantiopure furanone **4**, readily available through a palladium-catalyzed AAA in a dynamic kinetic asymmetric transformation, has shown its utility as a "chiral aldehyde" building block. The efficacy of this moiety to direct the diastereoselective assembly of substituted furanones was well demonstrated by its providing equivalent or superior results to known chiral butenolides under a variety of reactions. The crystalline natures of the products, amplified by the aryloxy group, simplified their purification, often requiring only recrystallization. Conjugate additions to butenolide **4** with stabilized nucleophiles, particularly nitroalkanes, gave complete diastereofacial control in forming the new stereogenic center. Cycloaddition reactions proceeded with high facial selectivity, often affording only a single diastereomer with up to four new stereogenic centers in outstanding yields. The excellent yields in these additions and the ability to run certain reactions neat with butenolide **4** has further illustrated its synthetic utility. The examples of TMM dipolar cycloadditions to the chiral butenolide **4** could not have given better results: complete control of regio- and diastereoselectivity in excellent yield. A short synthesis of Bayer compound **5** illustrated the utility of these building blocks for a pharmaceutical application.

The highly versatile synthetic strategy that takes advantage of this palladium-catalyzed AAA-derived "chiral aldehyde" equivalent has led to a total synthesis of (+)-brefeldin A (**6**). The synthesis was highly convergent and assembled the natural product from three components: commercial ethyl propiolate, a chiral six-carbon sulfone-ether fragment, and a highly functionalized cyclopentane core. The core fragment was readily assembled from a TMM-derived cyclopentenoid system, formed as a single diastereomer from a dipolar cycloaddition addition with the "chiral aldehyde" building block. After the introduction of the C(1)–C(3) upper side chain, through a diastereoselective addition reaction that gave access to either epimer at C(4), it is noteworthy that this was the first total synthesis to employ the newly developed *trans*-selective hydrosilylation protocol as a reduction method. The methodology was extended and used as a method for *trans*-selective alkyne reduction in the presence of other sensitive functional groups in model studies. The lower side chain **27** was made in several steps from the adduct of a regio- and enantioselective AAA reaction. This key reaction was notable for its low catalyst and ligand loading, its scalability, and its outstanding yield. After brief elaboration of the AAA-derived piece, it was efficiently introduced to the molecule's core in a *trans*-selective Julia olefination. The effort was completed in 18 linear steps with 6% overall yield from furfural **33**, an inexpensive and readily available starting material. Four of the stereogenic centers derive from a palladium-catalyzed DYKAT, while the remaining chirality was established by a palladium-catalyzed AAA reaction. In this synthesis, the potential for the design and synthesis of analogues is noteworthy, as the developed methodology allows access to either enantiomer of the core and lower side chain and allows reaction conditions to control the relative stereochemistry of the remaining stereogenic centers.

Experimental Section

(4*R*,5*S*)-4-(1′,1′-Bismethoxycarbonylmethyl)-5-(2-naphthoxy)dihydrofuran-2-one (7): Dimethyl malonate (72.7 mg, 0.550 mmol) and DMF (1.5 mL) were mixed, and sodium methoxide in methanol (2 N, 0.10 mL) was added. Butenolide *ent*-**4** (113 mg, 0.500 mmol) in DMF (1.0 mL) was added, and the solution was stirred at RT for 12 h. The mixture was diluted with methylene chloride (25 mL), washed with a saturated aqueous solution of ammonium chloride (0.5 N 25 mL), water (20 mL), and brine (20 mL), and after drying over sodium sulfate was concentrated in vacuo. Flash chromatography (diethyl ether/pet. ether 2:1) afforded lactone **7** as a white foam/gel (138 mg, 77 %). $[\alpha]_D = +137 \pm 1$ ($c = 4.00$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CHCl_3$): $\delta = 7.81$–7.77 (m, 3H), 7.51–7.38 (m, 3H), 7.20 (dd, $J = 9.0$, 2.2 Hz, 1H), 6.14 (d, $J = 2.4$ Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.68 (d, $J = 2.2$ Hz, 1H), 3.42–3.36 (m, 1H), 3.11 (dd, $J = 18.2$, 9.5 Hz, 1H), 2.62 ppm (dd, $J = 18.2$, 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CHCl_3$): $\delta = 173.7$, 167.5, 153.8, 134.0, 130.1, 129.7, 127.6, 126.6, 124.8, 118.6, 111.5, 103.1, 53.2, 53.0, 51.9, 41.4, 31.4 ppm; IR (film): $\tilde{\nu} = 3023$, 2956, 1797, 1734, 1631, 1600, 1511, 1467, 1436, 1254, 1213, 1161 cm^{-1}; HRMS: m/z calcd for $C_{19}H_{18}O_7$: 358.1052; found: 358.1061 $[M]^+$.

(4*R*,5*S*)-5-(Naphthoxy)-4-(1′-methyl-1′-nitroethyl)dihydrofuran-2-one (9): DBU (15.2 mg, 0.100 mmol) was added to a solution of 4-(2-naphthoxy)-butenolide *ent*-**4** (226 mg, 1.00 mmol) and 2-nitropropane (134 mg, 1.50 mmol) in methylene chloride (5.00 mL). The solution was stirred at RT for 1 h and was then subjected to flash chromatography (pet. ether/diethyl ether 1.5:1.0) to afford nitroalkane **9** as a white solid (293 mg, 93 %). M.p. 114–115 °C; $[\alpha]_D = +163 \pm 0.8$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.83$–7.79 (m, 3H), 7.52–7.42 (m, 3H), 7.22 (dd, $J = 8.8$, 2.5 Hz, 1H), 6.07 (d, $J = 2.9$ Hz, 1H), 3.39–3.35 (m, 1H), 3.05 (dd, $J = 18.3$, 10.0 Hz, 1H), 2.53 (dd, $J = 18.3$, 6.0 Hz, 1H), 1.71 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.8$, 153.6, 134.0, 130.3, 129.9, 127.7, 127.3, 126.8, 125.0, 118.5, 111.7, 102.1, 87.5, 50.0, 29.8, 24.3, 24.0 ppm; IR (film): $\tilde{\nu} = 2994$, 1796, 1631, 1600, 1542, 1511, 1468, 1348, 1252, 1213, 1158, 1069 cm^{-1}; HRMS: m/z calcd for $C_{17}H_{17}NO_5$: 315.1106; found: 315.1097 $[M]^+$.

{3*R*-[3α(1*R*,2*S*,5*R*)-3aα,4α,7α,7aα]}3α,4,7,7a-Tetrahydro-3-(2-naphthoxy)-4,7-ethanoisobenzofuran-1-(*3H*)-one (11): Butenolide *ent*-**4** (45.2 mg, 0.200 mmol) and 1,3-cyclohexadiene **10** (0.19 mL, 160 mg, 2.00 mmol) were heated neat at 150 °C in the microwave for 1 h. The mixture was concentrated in vacuo and diluted with methylene chloride (1.00 mL). Flash chromatography (pet. ether/diethyl ether 4:1) afforded cycloadduct **11** as a white solid as a single diastereomer (58.7 mg, 96 %). M.p. 94.5–95.0 °C; $[\alpha]_D = +234 \pm 1$ ($c = 3.40$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CHCl_3$): $\delta = 7.86$–7.77 (m, 3H), 7.50–7.47 (m, 1H), 7.44–7.40 (m, 1H), 7.20 (dd, $J = 9.0$, 2.4 Hz), 1H), 6.39 (t, $J = 7.2$ Hz, 1H), 6.34 (t, $J = 7.2$ Hz, 1H), 5.70 (d, $J = 1.7$ Hz, 1H), 3.20–3.18 (m, 1H), 3.06 (dd, $J = 9.6$, 3.5 Hz, 1H), 2.98–2.97 (m, 1H), 2.93–2.90 (m, 1H), 1.66–1.63 (m, 2H), 1.41–1.37 ppm (m, 2H); ^{13}C NMR (75 MHz, $CHCl_3$): $\delta = 177.5$, 154.1, 134.3, 134.1, 132.4, 129.9, 129.6, 127.6, 127.2, 126.6, 124.5, 118.7, 110.9, 104.7, 46.1, 44.9, 31.8, 31.7, 23.5, 23.2 ppm; IR (film): $\tilde{\nu} = 3053$, 2949, 2870, 1784, 1630, 1600, 1511, 1468, 1391, 1365, 1253, 1213, 1168, 1143 cm^{-1}; HRMS: m/z calcd for $C_{20}H_{18}O_3$: 306.1256; found: 306.1254 $[M]^+$.

(3*S*,4*R*,6a*S*)-4-(2-Naphthoxy)-3,3a,4,6a-tetrahydrofuro[3,4-c]pyrazol-6-one (16): A solution of diazomethane [ca. 2.00 mmol, prepared by treatment of 1-methyl-3-nitro-1-nitrosoguanidine (294 mg, 2.00 mmol) in diethyl ether (2.00 mL) with 20 % aqueous KOH solution (6 mL)] was added at 0 °C to a solution of butenolide **4** (45.2 mg, 0.200 mmol) in diethyl ether (2.00 mL). The solution was stirred for 2 h at −10 °C. The reaction mixture was quenched with SiO_2, diluted with CH_2Cl_2 (20 mL), filtered, and concentrated in vacuo. ^{1}H NMR spectroscopy (crude material) indicated a $dr > 4:1$ by comparison of the α-acetoxysulfone protons (major $\delta = 5.88$ ppm, minor $\delta = 6.14$ ppm). Flash chromatography (pet. ether/diethyl ether 1:3) gave product **16** as a white solid (38.4 mg, 76 %). ^{1}H NMR indicated the product was a single diastereomer. M.p. 172–173 °C; $[\alpha]_D = +77.8 \pm 0.2$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$–7.2 (m, 3H), 7.49–7.38 (m, 3H), 7.16 (dd, $J = 19.2$, 2.5 Hz, 1H), 5.88 (ddd, $J = 9.3$, 1.5, 1.0 Hz, 1H), 5.77 (d, $J = 1.5$ Hz, 1H), 5.14–5.04 (m, 1H), 4.97–4.89 (m, 1H), 3.27–3.19 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.3$, 153.4, 134.0, 130.2, 130.0, 127.7, 127.3, 126.9, 125.1, 118.3, 111.4, 105.0, 92.8, 84.0, 39.4 ppm; IR (film): $\tilde{\nu} = 3055$, 2982, 1790, 1631, 1599, 1511, 1350, 1215, 1163, 1076, 964 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{12}N_2O_3$: C 67.16, H 4.51; found: C 66.92, H 4.76.

(3*R*,3a*S*,6a*R*)-5-Benzyl-3-(2-naphthoxy)hexahydrofuro[3,4-c]pyrrol-1-one (18/19): TFA (0.5 M, 20 μL, 1.02 mg, 0.010 mmol) was added to a solution of butenolide **4** (22.6 mg, 0.100 mmol) and dipole precursor **17** (47.4 mg, 0.200 mmol) in methylene chloride (0.25 mL). The solution was stirred at −10 °C for 4 h. Flash chromatography (pet. ether/diethyl ether 1:1) gave two products with a crude $dr > 3:1$, as determined by ^{1}H NMR spectroscopy by comparison of the integrals of the major and minor signals for the anomeric center protons ($\delta = 5.92$ pm, major, $\delta = 6.21$ ppm, minor). The products were both white solids; **18** (25.4 mg, 71 %); **19** (7.6 mg, 21 %). The combined yield was 92 % (33.0 mg).

Compound 18: M.p. 50–51 °C; $[\alpha]_D = +121 \pm 0.1$ ($c = 1.50$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.79$–7.76 (m, 3H), 7.48–7.25 (m, 8H), 7.19 (dd, $J = 8.8$, 2.5 Hz, 1H), 5.92 (d, $J = 1.5$ Hz, 1H), 3.60 (abx, $J = 56.2$, 13.0 Hz, 2H), 3.35–3.30 (m, 2H), 3.18–3.08 (m, 2H), 2.51–2.45 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 177.9$, 153.9, 137.9, 134.2, 130.0, 129.7, 128.5, 128.4, 127.6, 127.3, 126.6, 124.6, 118.6, 111.0, 106.1, 58.6, 57.8, 57.1, 45.5, 43.7 ppm; IR (film): $\tilde{\nu} = 3060$, 2963, 2806, 1786, 1630, 1600, 1511, 1467, 1254, 1176, 1095, 977, 954 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{21}NO_3$: C 76.86, H 5.88; found: C 76.92, H 6.11.

Compound 19: M.p. 135–136 °C; $[\alpha]_D = +167 \pm 0.4$ ($c = 1.50$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.80$–7.76 (m, 3H), 7.48–7.25 (m, 8H), 7.19 (dd, $J = 8.8$, 2.5 Hz, 1H), 6.21 (d, $J = 6.6$ Hz, 1H), 3.80 (d, 13.0 Hz, 1H), 3.70 (dd, $J = 10.2$, 2.4 Hz, 1H), 3.60 (d, $J = 13.0$ Hz, 1H) 3.35–3.25 (m, 3H), 2.57 (dd, $J = 9.7$, 7.0 Hz, 1H), 2.33 ppm (dd, $J = 9.8$, 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 177.4$, 154.4, 138.9, 134.1, 130.0, 129.7, 128.5, 128.4, 127.6, 127.3, 126.6, 124.6, 118.6, 111.1, 100.9, 58.5, 57.2, 53.1, 45.2, 42.3 ppm; IR (film): $\tilde{\nu} = 3060$, 2963, 2806, 1786, 1630, 1600, 1511, 1467, 1254, 1176, 1095, 977, 954 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{21}NO_3$: C 76.86, H 5.88; found: C 77.00, H 6.12.

(3a*S*,6a*R*)-5-Methylenehexahydrocyclopenta[c]-furan-1-one (25): Sodium borohydride (95 mg, 2.50 mmol) was added to a solution of sodium hydroxide (200 mg, 5.0 mmol) in water (5 mL). After 5 min, *ent*-**4** (140 mg, 1.00 mmol) was added. The solution was stirred for 12 h at RT, and concentrated aqueous HCl (1 mL) was added dropwise (vigorous bubbling). The solution was stirred for an additional 1 h at RT, diluted with methylene chloride (20 mL), and washed with water (20 mL). The organic phase was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (pet. ether/diethyl ether 1:1) afforded product **25** as a clear oil (58 mg, 83 %). The data matched the data provided by Bayer company.[19] $[\alpha]_D = -58 \pm 0.1$ ($c = 3.80$ in $CHCl_3$); Bayer data[19]: $[\alpha]_D = -58.7$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.93$ (s, 2H), 4.45–4.42 (m, 1H), 4.04 (dd, $J = 9.2$, 2.8 Hz, 1H), 3.06–3.01 (m, 2H), 2.72–2.69 (m, 3H), 2.24–2.19 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 180.1$, 147.8, 108.2, 72.6, 43.9, 39.1, 38.7, 35.3 ppm; IR (film): $\tilde{\nu} = 3077$, 2917, 2851, 1766, 1667, 1480, 1432, 1374, 1171, 1125, 1050, 983 cm^{-1}; HRMS: m/z calcd for $C_8H_{10}O_2$: 138.0681; found: 138.0686.

BAY 36-7620 (5): A solution of lithium bis(trimethylsilyl)amide in THF (1.0 M, 0.220 mL, 36.8 mg, 0.220 mmol) was added under argon at −78 °C to a solution of substrate **25** (27.6 mg, 0.200 mmol) in toluene (1.00 mL). After 30 min at RT, a solution of 2-(bromomethyl)naphthalene (48.6 mg, 0.220 mmol) in toluene (1.00 mL) was added; then the bright yellow solution was stirred for 12 h at RT. The mixture was quenched with water (1.0 mL), and the organic layer was dried over sodium sulfate. Flash chromatography (pet. ether/diethyl ether 3:1) afforded product **26** as a colorless oil/gel (46.2 mg, 83 %). The data matched the data provided by the Bayer company.[19] $[\alpha]_D = -30 \pm 0.1$ ($c = 1.60$ in $CHCl_3$); Bayer data: $[\alpha]_D = -33.0$ ($c = 1.0$ in CH_2Cl_2);[19] ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.83$–7.78 (m, 3H), 7.67 (br s, 1H), 7.49–7.45 (m, 2H), 7.36 (dd, $J = 8.4$, 2.2 Hz, 1H), 4.92 (d, $J = 14.4$ Hz, 2H), 3.75 (dd, $J = 9.2$, 3.9 Hz, 1H), 3.64 (dd, $J = 9.2$, 7.7 Hz, 1H), 3.46 (d, $J = 13.7$ Hz, 1H), 2.92 (d, $J = 13.7$ Hz, 1H), 2.90–2.82 (m, 2H), 2.76–2.70 (m, 1H), 2.58 (d, $J = 6.1$ Hz, 1H), 2.25–2.21 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 181.6$, 147.1, 134.3, 133.4, 132.4, 128.4, 128.3, 127.8, 127.7, 126.6, 126.2, 125.8, 108.4, 72.0, 56.1, 43.6, 42.1, 41.8, 39.1 ppm; IR (film): $\tilde{\nu} = 3055$, 2971, 2911, 1765, 1664, 1600, 1508, 1431, 1376, 1175, 1138, 1049 cm^{-1}; HRMS: m/z calcd for $C_{19}H_{18}O_2$: 278.1307; found: 278.1302.

(*S*)-1-Methylprop-2-enyl 4-methoxyphenyl ether (29): Carbonate **34** (2.15 g, 16.5 mmol) was added under argon at 0 °C to a degassed solution of 4-methoxyphenol (1.86 g, 15.0 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (77.6 mg, 0.075 mmol), and ligand **3** (155.4 mg, 0.225 mmol) in toluene (400.0 mL). After stirring at 0 °C under argon for 12 h, the reaction mixture was directly subjected to chromatography (pet. ether/diethyl ether 10:1) to afford **29** as a clear oil (2.61 g, 95 %). The characterization data matched known values.[36] $[\alpha]_D = -7.5 \pm 0.1$ ($c = 5.40$ in $CHCl_3$); Lit. [23] $[\alpha]_D = -1.5 \pm 0.1$ ($c = 1.0$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.87$–6.77 (m, 4H), 5.93–5.87 (m, 1H), 5.23 (dd, $J = 17.3$, 1.3 Hz, 1H), 5.14 (dd, $J = 10.0$, 1.3 Hz, 1H), 4.68 (quintet, $J = 6.3$ Hz, 1H), 3.74 (s, 3H), 1.40 ppm (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 153.9$, 152.0, 139.5, 117.4, 115.6, 114.5, 114.4, 75.7, 55.6, 21.3 ppm; IR (film): $\tilde{\nu} = 2981$, 2933, 2834, 1506, 1465, 1442, 1228, 1039, 928, 826 cm^{-1}; $t_r(S) = 15.57$ min, $t_r(R) = 17.30$ min, 90 % *ee*, (Chiralcel OD, $\lambda = 254$ nm, hept/*i*PrOH 99.9:0.1).

2-(*S*)-(2-Naphthoxy)-5-oxo-2,5-dihydrofuran (*ent*-4): 2-Naphthol (3.00 g, 20.8 mmol) in methylene chloride (50 mL) was added at 0 °C under argon to a degassed solution of butenolide **1** (4.98 g, 25.0 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (538 mg, 0.520 mmol), *S*,*S*-ligand *ent*-**3** (1.08 g, 1.56 mmol), and tetrabutylammonium chloride hydrate (1.74 g, 6.25 mmol) in methylene chloride (150 mL) by the procedure reported by Trost and Toste.[6] The solution was stirred at 0–5 °C for 14 h. After concentration to 50 mL volume, it was subjected to chromatography on silica gel (pet. ether/diethyl ether 3:1) to afford butenolide *ent*-**4** as a white solid (2.84 g, 84 %). The characterization data were consistent with the literature data.[6] M.p. 73–74 °C; lit.[6] m.p. 72–74 °C; $[\alpha]_D = +328 \pm 1.2$ ($c = 1.1$ in CH_2Cl_2); lit.[6] $[\alpha]_D = +336$ ($c = 1.05$ in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.81$–7.77 (m, 3H), 7.58–7.42 (m, 4H), 7.23 (dd, $J = 9.0$, 2.7 Hz, 1H), 6.51 (d, $J = 1.3$ Hz, 1H), 6.36 ppm (dd, $J = 5.7$ Hz, 1.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.9$, 154.1, 149.8, 134.0, 130.2, 129.8, 127.6, 127.3, 126.7, 125.3, 124.9, 118.5, 111.5, 100.7 ppm; IR ($CHCl_3$): 3112, 3060, 1793, 1761, 1631, 1600, 1466, 1368 cm^{-1}; $t_r(S) = 11.8$ min; $t_r(R) = 15.2$ min (major for +328), 96 % *ee* (Chiralcel AD, $\lambda = 230$ nm, hept/*i*PrOH 9:1).

(3*S*,3a*S*,6a*R*)-5-Methylene-3-(2-naphthoxy)tetrahydrocyclopenta[c]furan-1-one (23a): Triisopropyl phosphite (491 μL, 416 mg, 2.00 mmol) was added to a solution of *ent*-**4** (2.26 g, 10.0 mmol), alkene **20a** (2.79 g, 15.0 mmol), and palladium(II) acetate (56.1 mg, 0.250 mmol) in toluene (100 mL). The solution was stirred at reflux for 12 h. After concentration in vacuo to 10 mL, flash chromatography (pet. ether/diethyl ether 3:1) gave product **23a** as a white solid (2.53 g, 90 %). ^{1}H NMR indicated the product was a single diastereomer. M.p. 74–74.5 °C; $[\alpha]_D = +235 \pm 0.3$ ($c = 2.00$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.79$–7.74 (m, 3H), 7.47–7.36 (m, 3H), 7.20 (dd, $J = 6.6$, 2.4 Hz, 1H), 5.90 (s, 1H), 4.97 (s, 2H), 3.39–3.34 (m, 1H), 3.20 (dd, $J = 9.1$, 3.0 Hz, 1H), 2.87–2.78 (m, 3H), 2.36 ppm (dd, $J = 16.0$, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 178.6$, 153.9, 146.7, 134.1, 130.0, 129.7, 127.6, 127.3, 126.6, 124.6, 118.6, 111.0, 108.8, 104.7, 46.0, 43.4, 36.2, 35.6 ppm; IR (film): $\tilde{\nu} = 2956$, 1787, 1631, 1600, 1511, 1467, 1252, 1214, 1158, 1121, 947, 932 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{16}O_3$: C 77.12, H 5.75; found: C 77.36, H 5.90.

(1*R*,2*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-formylcyclopentane-1-*N*,*O*-dimethylhydroxamine (52): Lactone *ent*-**31b** (797 mg, 2.00 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (488 mg, 5.00 mmol) made into a slurry in THF (20 mL) under argon and chilled to −10 °C. Isopropylmagnesium chloride in THF (4.8 mL, 987 mg, 9.60 mmol) was added dropwise over 5 min. The solution was stirred for 0.5 h at −10 °C and was then quenched with saturated aqueous ammonium chloride (20 mL). The mixture was extracted with methylene chloride (100 mL). The organic phase was dried over sodium sulfate, and concentrated in vacuo. The product was filtered through a plug of silica (diethyl ether/pet. ether 5:1 eluent) to afford a clear oil. The oil was dissolved in methylene chloride (20 mL) and treated with DBU (304 mg, 2.00 mmol). The solution was heated at reflux with stirring for 6 h, diluted with methylene chloride to a total volume of 100 mL, and washed with 1 N aqueous ammonium chloride solution (100 mL). The organic phase was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (diethyl ether/pet. ether 3:1) afforded aldehyde **52** as a clear oil (454 mg, 72 %, 2 steps). $[\alpha]_D = -10.1 \pm 0.1$ ($c = 4.00$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CHCl_3$): $\delta = 9.71$ (br s, 1H), 4.18–4.13 (m, 1H), 3.71 (s, 3H), 3.56–3.51 (m, 1H), 3.41–3.36 (m, 1H), 3.20 (s, 3H), 2.28–2.24 (m, 1H), 2.05–2.00 (m, 1H), 1.97–1.92 (m, 1H), 1.80–1.74 (m, 1H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (125 MHz, $CHCl_3$): $\delta = 202.6$, 174.5, 72.2, 61.2, 51.5, 39.1, 38.3, 35.4, 32.4, 25.7, 18.0, −4.8 ppm; IR (film): $\tilde{\nu} = 2931$, 2857, 2713, 1723, 1665, 1464, 1388, 1253, 1118, 1006, 838 cm^{-1}; HRMS: *m*/*z* calcd for $C_{14}H_{26}NO_4Si$: 300.1632; found: 300.1647 $[M-CH_3]^+$.

Ethyl (*S*)-4-[(1*R*,2R,4*R*)-4-(*tert*-butyldimethylsilyloxy)-2-(methoxymethylcarbamoyl)cyclopentyl]-4-hydroxybut-2-ynoate (53)

Compound 53a: A *n*-butyllithium solution (1 M in hexanes, 0.13 mL, 1.80 mmol) was added at −78 °C under argon to a solution of ethyl propiolate (177 mg, 1.80 mmol) in THF/HMPA 6:1 (7 mL). The solution was stirred for 1 h at −78 °C and became dark orange in color. Aldehyde **52** (378 mg, 1.20 mmol) in THF/HMPA solution (6:1, 7 mL) was added at −78 °C, and the solution was stirred for 4 h. The mixture was quenched with ammonium chloride solution (10 mL) and extracted with diethyl ether (3 × 20 mL), and the organic phase was dried over sodium sulfate and concentrated in vacuo. Crude ^{1}H NMR showed a 6.5:1.0 diastereomeric mixture of (4*S*)/(4*R*) by comparison of the α-hydroxymethyl proton signals of the Weinreb amide (major $\delta = 3.73$ ppm, minor $\delta = 3.70$ ppm). Flash chromatography (diethyl ether/pet. ether 3:1) first eluted ynoate **53a** as a colorless oil (364 mg, 73 %) and then ynoate **53b** as a colorless oil (75 mg, 15 %), contaminated with a small amount of **53a**. The combined yield was 88 % (439 mg). $[\alpha]_D = -14.8 \pm 0.2$ ($c = 3.40$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CHCl_3$): $\delta = 4.58$–4.56 (m, 1H), 4.32–4.28 (m, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 3.78 (d, $J = 5.4$ Hz, 1H), 3.73 (s, 3H), 3.19 (s, 3H), 3.09–3.02 (m, 2H), 2.38–2.34 (m, 1H), 1.82–1.64 (m, 3H), 1.28 (t, $J = 7.1$ Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 ppm (s, 3H); ^{13}C NMR (125 MHz, $CHCl_3$): $\delta = 175.6$, 153.2, 86.4, 77.2, 71.8, 64.3, 62.0, 61.3, 44.6, 41.6, 40.5, 37.5, 32.6, 25.8, 17.9, 13.9, −4.8 ppm; IR (film): $\tilde{\nu} = 3400$, 2938, 2857, 2235, 1714, 1662, 1462, 1389, 1249, 1117, 1058, 1006 cm^{-1}; HRMS: *m*/*z* calcd for $C_{19}H_{32}NO_6Si$: 398.1999; found: 398.2008 $[M-CH_3]^+$.

Compound 53b: A *n*-butyllithium solution (1 M in hexanes, 0.13 mL, 1.80 mmol) was added at −78 °C under argon to a solution of ethyl propiolate (177 mg, 1.80 mmol) and magnesium bromide (331 mg, 1.80 mmol) in DME (5.00 mL). The solution was stirred for 1 h at −78 °C and became dark orange in color. Aldehyde **52** (378 mg, 1.20 mmol) in DME (5 mL) was added at −78 °C, and the solution was stirred for 4 h. The mixture was quenched with ammonium chloride solution (10 mL) and extracted with diethyl ether (3 × 20 mL), and the organic phase was dried over sodium sulfate and concentrated in vacuo. Crude ^{1}H NMR showed a 1.0:6.0 diastereomeric mixture of (4*S*)/(4*R*) by comparison of the α-hydroxymethyl proton signals of the Weinreb amide (minor $\delta = 3.73$ ppm, major $\delta = 3.70$ ppm). Flash chromatography (diethyl ether/pet. ether 3:1) first eluted ynoate **53a** as a colorless oil (65 mg, 13 %) and then ynoate **53b** as a colorless oil (389 mg, 78 %), contaminated with a trace amount of **53a**. The combined yield was 91 % (454 mg). $[\alpha]_D = -17.4 \pm 0.3$ ($c = 0.80$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CHCl_3$): $\delta = 4.34$–4.28 (m, 2H), 4.20 (q, $J = 7.2$ Hz, 2H), 3.78 (d, $J = 5.4$ Hz, 1H), 3.70 (s, 3H), 3.19 (s, 3H), 3.09–3.02 (m, 2H), 2.38–2.34 (m, 1H), 1.82–1.64 (m, 3H), 1.28 (t, $J = 7.1$ Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 ppm (s, 3H); ^{13}C NMR (125 MHz, $CHCl_3$): $\delta = 175.6$, 153.2, 86.6, 77.2, 72.0, 65.2, 62.0, 62.0, 44.6, 41.6, 40.5, 37.5, 32.6, 25.8, 17.9, 13.9, −4.8 ppm; IR (film): $\tilde{\nu} = 3400$, 2938, 2857, 2235, 1714, 1662, 1462, 1389, 1249, 1117, 1058, 1006 cm^{-1}; HRMS: *m*/*z* calcd for $C_{19}H_{32}NO_6Si$: 398.1999; found: 398.2006 $[M-CH_3]^+$.

Ethyl (*E*)-(*R*)-4-[(1*R*,2*R*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-2-(methoxymethylcarbamoyl)cyclopentyl]-4-hydroxybut-2-enoate (56a): The ruthenium catalyst (2.10 mg, 0.0040 mmol) was added at 0 °C under argon to a methylene chloride solution (10 mL) of alkyne **53a** (165 mg, 0.400 mmol) and triethoxysilane (78.9 mg, 0.480 mmol). The mixture was allowed to warm to RT with stirring over 2 h. Cesium fluoride (72.9 mg, 0.480 mmol) and ethanol (1.00 mL) were added, and the solution was stirred at RT for 12 h. The mixture was diluted with methylene chloride (50 mL) and washed with water (2 × 30 mL) and brine (30 mL). The organic phase was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (diethyl ether/pet. ether 4:1) afforded enoate **56a** as a clear oil (153 mg, 92 %). $[\alpha]_D = -16.2 \pm 0.2$ ($c = 1.80$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CHCl_3$): $\delta = 6.92$ (dd, $J = 15.6$, 5.4 Hz, 1H), 6.05 (d, $J = 15.6$ Hz, 1H), 4.41–4.39 (m, 1H), 4.27–4.22 (m, 1H), 4.20 (d, $J = 7.0$ Hz, 2H), 3.69 (s, 3H), 3.21 (s, 3H), 3.01–2.95 (m, 1H), 2.93–2.90 (m, 1H), 2.52 (d, $J = 4.7$ Hz, 1H), 2.34–2.30 (m, 1H), 1.69–1.62 (m, 3H), 1.29 (t,

$J=7.1$ Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (125 MHz, $CHCl_3$): $\delta=166.4$, 164.8, 148.1, 121.2, 71.9, 71.3, 61.3, 60.4, 44.6, 41.0, 40.5, 36.1, 29.7, 25.8, 18.0, 14.2, −4.8 ppm; IR (film): $\tilde{\nu}=3429$, 2928, 2856, 1719, 1654, 1464, 1383, 1257, 1175, 1116 cm^{-1}; HRMS: m/z calcd for $C_{20}H_{37}NO_6Si$: 400.2156; found: 400.2176 $[M-CH_3]^+$.

Ethyl (*E*)-(*R*)-4-(*tert*-butyldimethylsilyloxy)-{(1*R*,2*R*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-2-[(*E*)-(*S*)-6-(4-methoxyphenoxy)hept-1-enyl]cyclopentyl}but-2-enoate (61): A solution of tetrazole **17** (93.7 mg, 0.225 mmol) in DME (1.0 mL) was added at −78 °C under argon to a solution of potassium hexamethyldisilylazide (49.9 mg, 0.250 mmol) in DME (1.00 mL). After the mixture had been kept for 1 h at −78 °C, a solution of aldehyde **51** (70.6 mg, 49.9 mg) in DME (0.5 mL) was added; the reaction mixture was stirred for 1 h at −78 °C. The solution was allowed to warm to RT, stirred for 16 h at RT, poured into brine (5.0 mL), and extracted with diethyl ether (3×5 mL). The organic phase was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (pet. ether/diethyl ether 8:1) afforded product **61** as a clear oil (72 mg, 81 %) The *E*/*Z* ratio as determined by ^{1}H NMR spectroscopy was 12:1. $[\alpha]_D=+5.5\pm0.1$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=6.85$ (dd, $J=15.6$, 3.0 Hz, 1H), 6.83 (s, 4H), 5.90 (d, $J=15.6$ Hz, 1H), 5.38–5.35 (m, 2H), 4.26–4.16 (m, 5H), 3.77 (s, 3H), 2.33–2.28, (m, 1H), 2.03–1.98 (m, 3H), 1.98–1.93 (m, 1H), 1.89–1.82 (m, 1H), 1.75–1.67 (m, 2H), 1.58–1.40 (m, 4H), 1.21 (t, $J=6.4$ Hz, 3H), 0.92 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 6H), 0.00 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=166.4$, 151.1, 144.7, 134.5, 129.8, 128.4, 125.9, 119.8, 117.4, 114.6, 74.4, 72.8, 71.2, 60.3, 55.7, 49.2, 43.6, 42.6, 36.0, 34.1, 32.4, 29.7, 25.8, 19.8, 18.1, 18.0, −4.0, −4.3, −4.8, −4.9 ppm; IR (film): $\tilde{\nu}=2929$, 2856, 1722, 1655, 1506, 1463, 1370, 1229, 1166, 1106, 1039 cm^{-1}; HRMS: m/z calcd for $C_{37}H_{64}O_6Si_2$: 660.4241; found: 660.4238 $[M]^+$.

(*E*)-(*R*)-4-(*tert*-Butyldimethylsilyloxy)-{(1*R*,2*R*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-2-[(*E*)-(*S*)-6-hydroxyhept-1-enyl]cyclopentyl}but-2-enoic acid (62): Ceric ammonium nitrate (137 mg, 0.250 mmol) in water (0.500 mL) was added at 0 °C to a solution of substrate **61** (66.1 mg, 0.100 mmol) in acetone (2.00 mL). The solution was stirred for 30 min at 0 °C. The mixture was extracted with diethyl ether (2×10 mL), and the organic phase was dried over sodium sulfate and concentrated in vacuo. The crude mixture was filtered through a thin plug of silica with diethyl ether as eluent. Free OH: ^{1}H NMR (500 MHz, $CHCl_3$): $\delta=6.92$ (dd, $J=15.7$, 5.3 Hz, 1H), 6.18 (d, $J=15.7$ Hz, 1H), 5.44–5.40 (m, 2H), 4.24–4.21 (m, 1H), 4.21–4.18 (m, 1H), 4.20 (q, $J=7.2$ Hz, 2H), 3.86–3.82 (m, 1H), 2.32–2.27 (m, 1H), 2.07–1.96 (m, 4H), 1.82–1.77 (m, 1H), 1.60–1.55 (m, 1H), 1.52–1.40 (m, 5H), 1.24 (d, $J=6.1$ Hz, 3H), 0.98 (s, 9H), 0.92 (t, $J=7.2$ Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 6H), 0.03 ppm (s, 3H); IR (film): $\tilde{\nu}=3360$, 2930, 2858, 1692, 1659, 1472, 1405, 1250 cm^{-1}; HRMS: m/z calcd for $C_{26}H_{49}O_5Si_2$: 497.3118; found: 497.3114 $[M-C_4H_9]^+$.

The concentrated crude mixture was dissolved in a THF/MeOH mixture (2:1, 3.00 mL). Aqueous sodium hydroxide (1 N, 1 mL) was added, and the mixture was stirred at 60 °C for 1 h. The mixture was acidified with 1 N sodium hydrogen sulfate solution (10 mL), extracted with diethyl ether (3×5 mL), and dried over sodium sulfate. Flash chromatography (methanol/chloroform 3:97) afforded acid **62** as a clear oil (40.6 mg, 77 %, 2 steps). $[\alpha]_D=-9.6\pm0.5$ ($c=0.30$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CHCl_3$): $\delta=7.01$ (dd, $J=15.6$, 5.1 Hz, 1H), 5.95 (d, $J=15.7$ Hz, 1H), 5.38–5.32 (m, 2H), 4.25–4.22 (m, 1H), 4.21–4.18 (m, 1H), 3.86–3.82 (m, 1H), 2.32–2.27 (m, 1H), 2.07–1.96 (m, 4H), 1.82–1.77 (m, 1H), 1.59–1.54 (m, 1H), 1.52–1.40 (m, 5H), 1.21 (d, $J=6.2$ Hz, 3H), 0.95 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 6H), 0.03 ppm (s, 3H); ^{13}C NMR (75 MHz, $CHCl_3$): $\delta=170.2$, 153.6, 134.7, 129.8, 119.0, 72.9, 72.2, 68.2, 49.5, 43.6, 42.9, 38.5, 36.0, 32.4, 25.9, 25.8, 25.7, 23.4, 18.1, −3.9, 4.8 ppm; IR (film): $\tilde{\nu}=3360$, 2930, 2858, 1699, 1659, 1472, 1410, 1256, 1120, 836, 775 cm^{-1}; HRMS: m/z calcd for $C_{24}H_{45}O_5Si_2$: 469.2805; found: 469.2800 $[M-C_4H_9]^+$.

(5*E*,13*E*)-(2*S*,3a*R*,4*R*,10*S*,14a*S*)-2,4-Bis-(*tert*-butyldimethylsilyloxy)-9-methyl-1,2,3,3a,4,9,10,11,12,14a-decahydro-8-oxacyclopentacyclotridecen-7-one (63): Triethylamine (7.65 mg, 0.075 mmol) and 2,4,6-trichlorobenzoyl chloride (17.1 mg, 0.070 mg) were added to a solution of substrate **62** (26.4 mg, 0.050 mmol) in THF (0.500 mL). The solution was stirred at RT for 3 h. That mixture was diluted with toluene (6.0 mL) and added dropwise over 3 h to a solution of 4-dimethylaminopyridine (30.5 mg, 0.250 mmol) in toluene (10.0 mL) at reflux. The solution was stirred at reflux for an additional 8 h. The mixture was diluted with diethyl ether (20 mL). The organic phase was washed with aqueous HCl solution (0.25 N, 20 mL) and saturated aqueous sodium bicarbonate solution (20 mL) and then dried over sodium sulfate. After concentration in vacuo, chromatography (pet. ether/diethyl ether 20:1) afforded lactone **63** as a clear oil (16.8 mg, 66 %). $[\alpha]_D=+40.2\pm0.5$ ($c=0.50$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CHCl_3$): $\delta=7.29$ (dd, $J=15.5$, 3.1 Hz, 1H), 5.86 (dd, $J=15.5$, 2.0 Hz 1H), 5.63 (ddd, $J=15.6$, 10.4, 4.5 Hz, 1H), 5.27 (dd, $J=15.6$, 5.5 Hz, 1H), 4.92–4.85 (m, 1H), 4.21–4.18 (m, 1H), 4.03–4.00 (m, 1H), 2.28–2.21 (m, 1H), 2.07–1.94 (m, 4H), 1.88–1.79 (m, 2H), 1.75–1.70 (m, 1H), 1.56–1.45 (m, 3H), 1.27 (d, $J=6.1$ Hz, 3H), 1.26–1.23 (m, 1H) 0.93 (s, 9H), 0.85 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 ppm (s, 3H); ^{13}C NMR (75 MHz, $CHCl_3$): $\delta=166.4$, 152.5, 137.3, 129.3, 118.0, 76.3, 72.8, 71.4, 52.8, 43.8, 43.6, 42.0, 34.1, 31.8, 26.7, 25.8, 20.9, 18.1, 18.0, −4.1, −4.8, −4.9 ppm; IR (film): $\tilde{\nu}=2929$, 2857, 1716, 1646, 1410, 1255, 1122, 1078, 1004, 967, 837, 774 cm^{-1}; HRMS: m/z calcd for $C_{28}H_{52}O_4Si_2$: 508.3404; found: 508.3414 $[M]^+$.

(+)-Brefeldin A (6): A solution of TBAF (1.0 M in THF, 100 μL, 26.1 mg, 0.100 mmol) was added at 0 °C to a solution of substrate **63** (16.7 mg, 0.0328 mmol) in THF (1 mL). The solution was stirred at 0 °C for 4 h. The mixture was diluted with ethyl acetate (10 mL) and washed with water (10 mL), and the organic phase was concentrated in vacuo. Flash chromatography (ethyl acetate/pet. ether 5:1) afforded (+)-brefeldin A (**6**) as a white solid (8.1 mg, 77 %). The rotation and spectral data matched those observed for natural (+)-brefeldin A. M.p. >200 °C; lit.[18] m.p. 202–203 °C; $[\alpha]_D=+89.6\pm0.5$ ($c=0.40$ in MeOH); lit.[18] $[\alpha]_D=+91.2\pm0.4$ ($c=0.50$ in MeOH); ^{1}H NMR (500 MHz, $CHCl_3$): $\delta=7.45$ (dd, $J=15.5$, 3.0 Hz, 1H), 5.80 (dd, $J=15.5$, 2.0 Hz, 1H), 5.70 (ddd, $J=15.0$, 10.5, 4.5 Hz, 1H), 5.27 (dd, $J=15.6$, 5.5 Hz, 1H), 4.79–4.75 (m, 1H), 4.21–4.18 (m, 1H), 4.02 (ddd, $J=9.5$, 3.1, 2.0 Hz, 1H), 2.37 (quintet, 1H), 2.10 (ddd, $J=13.5$, 8.4, 5.2 Hz, 1H), 2.02–1.97 (m, 2H), 1.88–1.72 (m, 5H), 1.58–1.50 (m, 1H), 1.46–1.40 (m, 1H), 1.23 (d, $J=6.3$ Hz, 3H), 0.89–0.85 ppm (m, 1H); ^{13}C NMR (75 MHz, $CHCl_3$): $\delta=168.4$, 155.2, 138.1, 131.4, 117.8, 76.6, 73.2, 73.0, 53.2, 45.5, 44.1, 41.8, 35.0, 33.0, 28.0, 21.1 ppm; IR (film): $\tilde{\nu}=3395$, 2924, 2852, 1711, 1693, 1638, 1448, 1353, 1259, 1119 cm^{-1}; HRMS: m/z calcd for $C_{24}H_{46}O_4$: 280.1675; found: 260.1668 $[M]^+$.

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