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Regioselective and diastereoselective synthesis of highly substituted cyclopentanes

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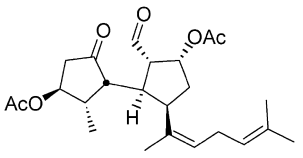
Abstract—Highly substituted cyclopentane rings are present in a wide range of targets, and the efficient synthesis of such compounds constitutes a continuing challenge to organic synthesis. We present two complementary approaches to the regio- and diastereoselective synthesis of highly substituted cyclopentane structures. In both cases, a non-symmetrically disposed norbornene is employed as a common intermediate. One strategy relies on the Lewis acid-catalyzed ring opening of an anhydride, while the other employs production of a bicyclic lactone followed by its selective functionalization.

1. Introduction

The stereo- and regioselective functionalization of cyclopentane rings has been a longstanding challenge in synthetic chemistry, both as a necessary part of natural product syntheses, and in the construction of novel cyclopentanoid structures. For example, a variety of recently isolated natural products incorporate highly substituted cyclopentane substructures, and constitute novel challenges to synthetic organic chemistry. Dilkamural (**1**), an antimicrobial agent, was recently isolated from a brown sea algae found near Japan.[1] Analysis of the extracts from tart cherries (*Prunus cerasus*) revealed a highly oxygenated cyclopentane ring natural product **2**, which was found to possess antioxidant properties.[2] Ottelione A (**3**) was recently isolated from an Egyptian freshwater plant, and subsequently found to have significant cytotoxicity against mouse tumor cell lines.[3] The cyclopentane ring embedded in these molecules is highly substituted, and the regio- and stereochemical positioning of that substitution is important to each compound's biological activity. Likewise, highly substituted cyclopentane rings are central components of a wide range of 'unnatural' products. Consequently, the development of new methodology for the construction of such compounds is an active area of research.[4]



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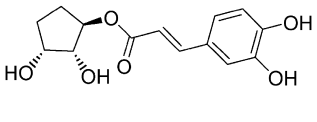

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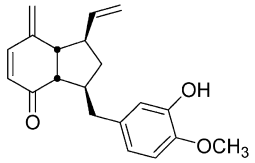

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We have been engaged in the synthesis of highly substituted oligocyclopentanes, as relatively unexplored fundamental organic materials, and as potential scaffolds for molecular recognition. In particular, we recently reported the synthesis of **4**, a compound accessible from norbornene in nine synthetic steps.[5] Compound **4** was found to bind lipid A (**5**), the conserved head group of bacterial lipopolysaccharide, with a dissociation constant (K_D) of 0.6 μM, approaching the affinity displayed by natural products such as polymyxin B1 (K_D=370 nM) for this pharmaceutically important target.[6] In our initial synthetic efforts, we focused on synthetic speed and simplicity, at the cost of customizability. Since the ability of this class of compounds to function as receptors was completely unknown, *meso*-tetrol **6** was targeted as a key intermediate. Such rapid access to the basic scaffold allowed us to begin examining compounds of this structural class, and determine their

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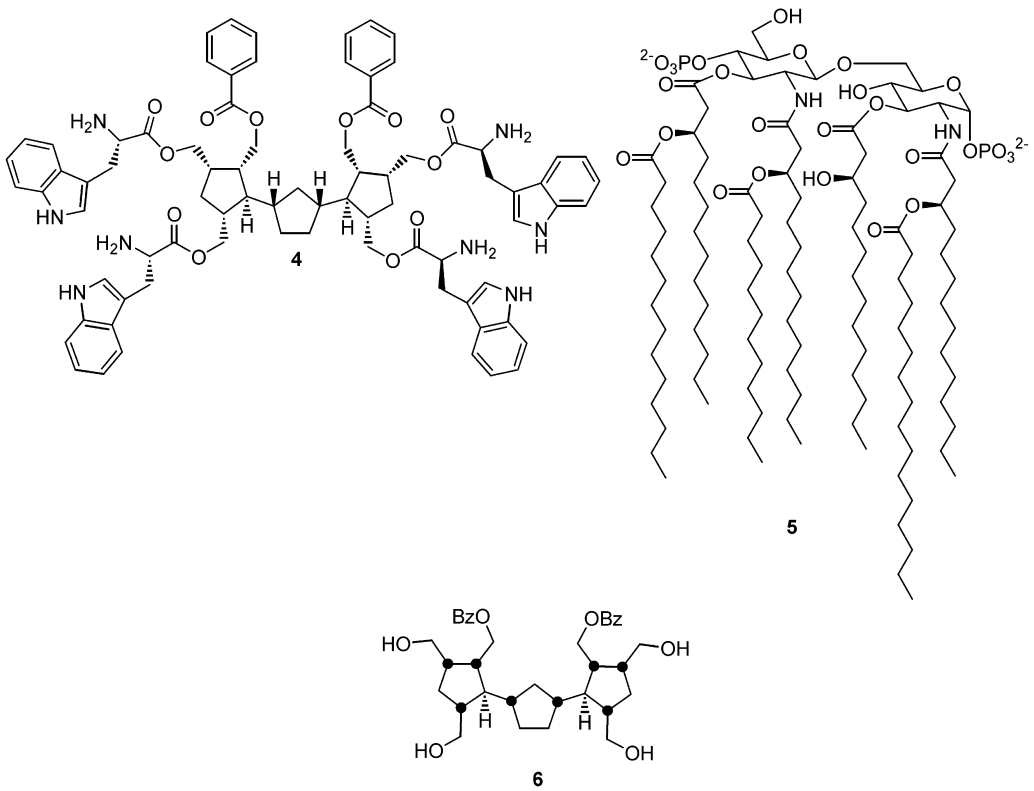
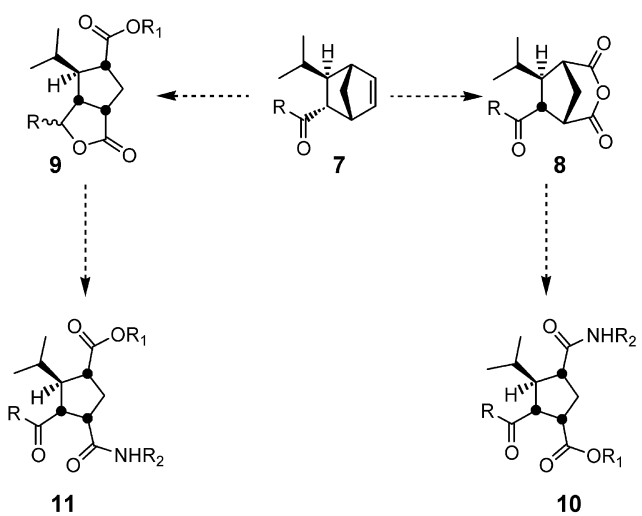
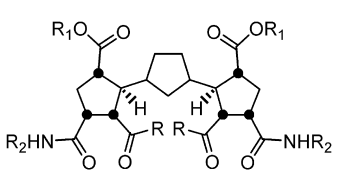


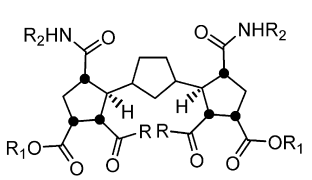
suitability for further study.[7] In order to probe in depth the effect of substitution pattern on molecular recognition ability, however, we required a synthetic approach that would allow us to generate non-symmetrically substituted *tert*-cyclopentane scaffolds.

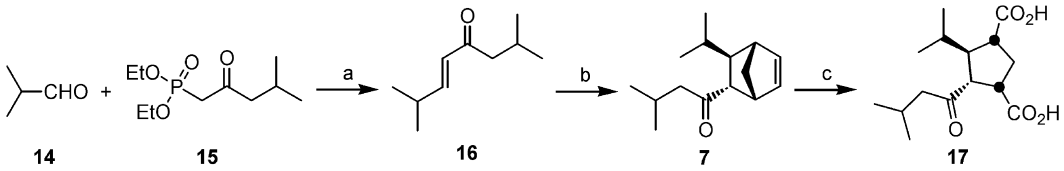
Stereoselective and regioselective functionalization of cyclopentanes is problematic relative to the analogous functionalization of cyclohexanes because of the greater conformational mobility[8] (due to pseudorotation[9]) of the cyclopentane ring. Therefore, an attractive starting point for the generation of highly substituted, desymmetrized cyclopentane rings is the regioselective functionalization of bicyclo-[2.2.1]-systems, because of their rigidity. Typically, two general approaches have been applied to the transformation of such bicyclic molecules into substituted cyclopentanes: first, nucleophilic ring opening of *meso*-[2.2.1]-anhydrides,[10] and second, ring-opening/cross-olefin metathesis of [2.2.1]-bicyclic systems.[11] In the first case, a chiral Lewis acid, auxiliary, or nucleophile is employed to provide diastereoselectivity; in the second, bias is derived via a chiral metathesis catalyst. While each of these methods can be highly useful, they each have limitations with regard to substrate scope. Thus, additional strategies in this area are needed. We envisioned two approaches that would employ neighboring heteroatom functionality to assist in the diastereoselective and regioselective transformation of a non-*meso* bicyclic system into a highly substituted cyclopentane, via either nucleophilic addition to an anhydride formed in situ, or selective transformation of a bicyclic lactone (Scheme 1). For these studies, compounds **10** and **11** were targeted as models for the more complex **12** and **13**.



Scheme 1.







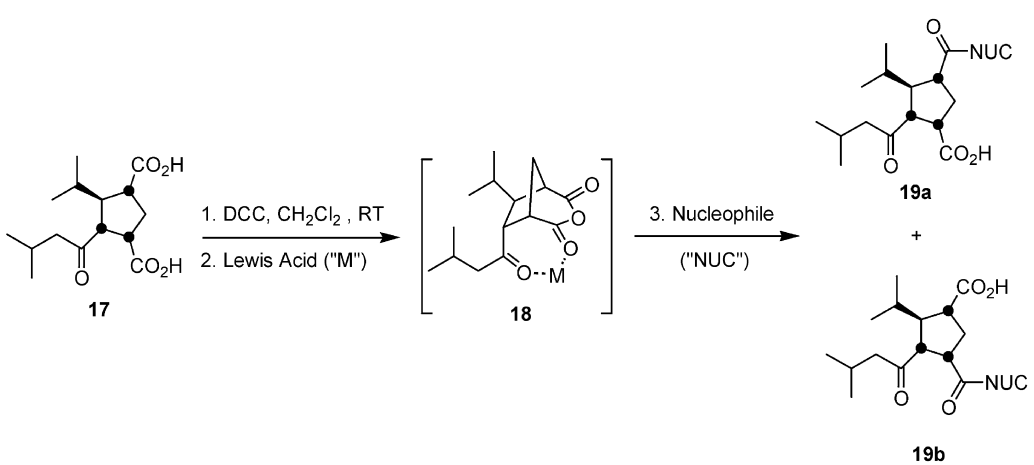
Scheme 2. Synthesis of diacid **17**. (a) LiCl, DIPEA, CH_3CN, rt (79%, >95:5 *E*/*Z*); (b) Me_3Al (0.05 equiv.) 10 min, then $AlCl_3$ (0.5 equiv.), 10 min, CH_2Cl_2, 0°C, then: cyclopentadiene (10 equiv.), −78°C, (81%, 94:6 *endo*/*exo*); (c) (i) O_3, PPh_3, CH_2Cl_2, 0°C to rt, (ii) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$ (2.0 M in H_2O) in 80% *tert*-butanol/2-methyl-2-butene (75% yield).

2. Results and discussion

The synthesis of the substituted norbornene **7**, in which R=$-CH_2CH(CH_3)_2$, began with Horner–Wadsworth–Emmons olefination of isobutyraldehyde (**14**), with the known β-ketophosphonate **15**[12] under Roush–Masamune conditions (LiCl, DIPEA, CH_3CN).[13] This provided the known ketone **16**[14] in 79% yield and >95:5 *E*/*Z* olefin selectivity (Scheme 2). Treatment of **16** with excess cyclopentadiene under Diels–Alder reaction conditions previously reported by our laboratory [Me_3Al (0.05 equiv.)/$AlCl_3$ (0.5 equiv.)][15] afforded ketone **7** in 90% yield and 94:6 *endo*/*exo* diastereoselectivity. While scaling up this cycloaddition (>1 g of **16**), we found that removal of the nitrobenzene provided in the commercial solutions of $AlCl_3$[16] was difficult either by reduction of solvent in vacuo, or by removal via flash chromatography. Since azeotropic removal of nitromethane with heptane is facile,[17] we instead substituted solutions of $AlCl_3$ in CH_3NO_2. Initially, we employed a one-step oxidative cleavage[18] of the olefin in **7** with $RuCl_3{\cdot}H_2O$ and $NaIO_4$ that afforded the di-acid **17** in quantitative crude yield; however, the product was highly colored, suggesting the presence of residual ruthenium salts. Despite many attempts, we were unable to completely purify this material to our satisfaction. Consequently, we opted for a two-step oxidative cleavage procedure. First, ozonolytic cleavage of **7**, followed by a reductive work-up with PPh_3 afforded an intermediate di-aldehyde. This was not isolated, but treated directly under Lindgren conditions[19] ($NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, in 80% *tert*-butanol/2-methyl-2-butene) to afford **17** in 75% yield from **7**.

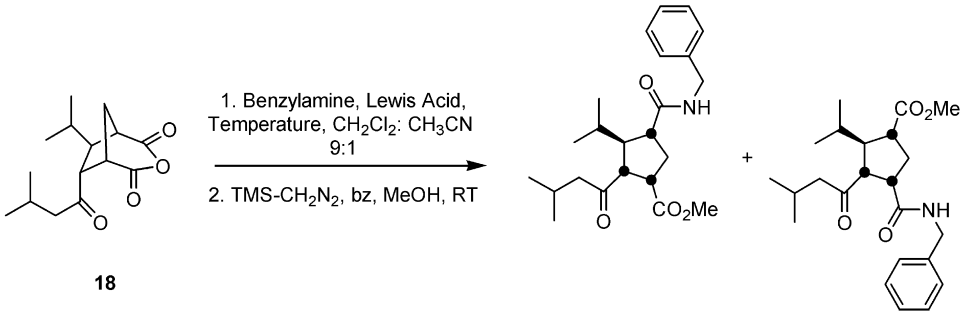
With the diacid **17** in hand, we were now ready to synthesize the essential anhydride intermediate **8**, in which R=$-CH_2CH(CH_3)_2$. Subsequent treatment of **8** with a Lewis acid was anticipated to preferentially coordinate the ketone and the proximal anhydride carbonyl to yield a seven-membered ring chelate (**18**, Scheme 3). Although 5- and 6-membered chelates have found extensive use in synthetic chemistry, 7-membered chelates are much less common. However, they are not unknown; for example, a 7-membered lithium chelate was posited as contributing to the high selectivity observed for an enolate alkylation in the Evans group's total synthesis of ionomycin.[20] Numerous solid-state structures of 7-membered chelates are also known.[21] Given the steric bulk of the *iso*-valeryl group in **18**, the sterics of a given Lewis acid's ligand sphere, and electronic activation of the distal carbonyl to nucleophilic attack, we reasoned that a chelate should bias the attack of an incoming nucleophile, such that **19a** would be formed preferentially over **19b**. Anhydride formation was achieved by treating **17** with DCC in CH_2Cl_2 at rt.[22] The reaction was filtered through Celite and used without further purification. A Lewis acid was then added, allowing formation of the presumed chelated species **18**.

Treatment of the putative anhydride **18** with benzylamine under a variety of conditions (vide infra), and subsequent esterification of the resulting acids with TMS–diazomethane afforded two esters, tentatively identified based on the above mechanistic model as **20** and **21**. No other products are observed following work-up of the reaction, suggesting that the remainder of the mass balance is unreacted **18** (converted to diacid **17** via the workup procedure). The integration of the regioisomeric methyl resonances, from a 400-MHz ^1H NMR of the crude reaction mixture, was used to determine the selectivity of the reaction in each case. As shown in Table 1, the iso-valeryl group of the ketone was sterically demanding enough to



Scheme 3. Proposed regioselective opening of anhydride **18**.

Table 1. Nucleophilic addition of benzylamine to anhydride **18** in the presence or absence of Lewis acids



18 **20** **21**

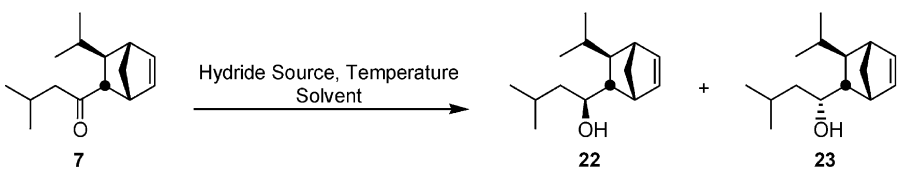
Entry	Temperature (°C)	Lewis acid (equiv.)	Regioselectivity (20:21)	Yield (%, from **17**)
1	25	None	1.8/1	40
2	25	LiCl (1.2)	3.4/1	72
3	4	LiCl (1.2)	4.5/1	65
4	−20	LiCl (1.2)	5.0/1	59
5	25	$MgCl_2$ (1.2)	5.3/1	64
6	4	$MgCl_2$ (1.2)	4.5/1	37
7	−20	$MgCl_2$ (1.2)	3.5/1	42
8	4	$MgCl_2$ (2.5)	2/1	56
9	4	$(Cp)_2TiCl_2$ (1.2)	2.6/1	29
10	25	$Sc(OTf)_3$ (1.2)	1.5/1	21

promote a modest amount of regioselectivity in the absence of a Lewis acid, affording **20**:**21** in a 1.8:1 ratio (entry 1). Best results with respect to selectivity were obtained using 1.2 equiv. of $MgCl_2$ as the Lewis acid at room temperature, which allowed for the selective formation of **20** in a 5.3:1 ratio. Increasing the amount of $MgCl_2$ or reducing the temperature resulted in reduced selectivity. At lower temperatures (−20°C), LiCl was found to provide better selectivity than $MgCl_2$. We speculate that at −20°C, the lower vibrational energy of **18** favors chelation by the smaller Li(+) ion, while the less compact (or, alternatively, more conformationally mobile) structure expected for **18** at higher temperatures favors coordination to Mg(2+).

The nucleophilic attack on **18** was predicated on the idea that the ketone and its pendant functionality could be used to relay regiochemical control, albeit transiently, to the rest of the cyclopentane ring system. We envisioned that a complimentary strategy could relay regio- and stereochemical information through covalent attachment to the ketone, via formation of a lactone. In addition to providing access to **11**, the regiochemically opposite substitution pattern to **10**, execution of such a strategy would potentially permit independent verification of the assignment of compounds **20** and **21**.

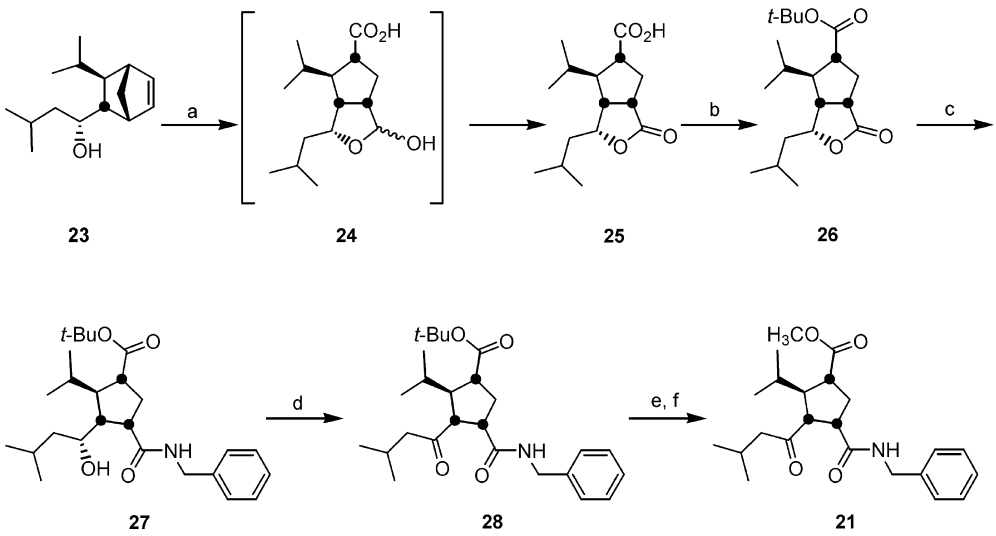
Synthetic progress towards a lactone analogous to **9** began with reduction of the ketone moiety present in cycloadduct **7** to afford a mixture of diastereomeric alcohols (**22** and **23**). As shown in Table 2, a series of hydride sources and conditions were probed to promote this reduction. The diastereoselectivity of the reaction, albeit modest in all cases, was found to be independent of the size of the hydride source (entry 1 vs. entry 4). However, the temperature at which the reduction was performed was found to dramatically affect which diastereomer formed preferentially (entry

Table 2. Hydride reduction of **7**



7 **22** **23**

Entry	Hydride source	Solvent	Temperature (°C)	Yield (%)	Selectivity (**22**:**23**)
1	LAH	THF	0	63	1.8:1
2	LAH	THF	−78	76	1.4:1
3	DIBAL-H	THF	0	70	2.2:1
4	L-Selectride	THF	−78 to 0 (4 h)	72	2.4:1
5	L-Selectride	THF	−78 to 0 (15 min)	80	1:1.6
6	L-Selectride	THF	25	76	1:2.4
7	L-Selectride	Et_2O	25	32	1:3



Scheme 4. Alternative synthesis of amide **21**. (a) $RuCl_3{\cdot}H_2O$, $NaIO_4$, 2/2/3 $CCl_4/CH_3CN/H_2O$, rt; (b) DIC, DMAP, *tert*-butanol, CH_2Cl_2, rt (60% yield from **23**); (c) (i) $(CH_3)_3Al$, benzylamine, benzene, rt, (ii) **26**, benzene, 40°C (68% yield); (d) Dess–Martin periodinane, CH_2Cl_2, rt (54% yield); (e) *p*-TsOH, benzene, reflux; (f) $TMSCH_2N_2$, benzene/MeOH 72:28, rt (81% yield from **28**).

4 vs. entry 6). Initially, our assignments of **22** and **23** were based on analysis of their ^1H NMR spectra, and of their physical properties. Single crystal X-ray crystallographic analysis of the more polar compound confirmed that **22** was the β-diastereomeric alcohol as originally assigned.

After chromatographic separation of the diastereomeric alcohols **22** and **23**, each diastereomer was independently submitted to the chemical transformations presented in Scheme 4.[23] Oxidation of **23** with $RuCl_3{\cdot}H_2O$ and $NaIO_4$, in the mixed solvent system of 2:2:3 $CCl_4/CH_3CN/H_2O$ afforded lactone **25** directly. Lactone **25** presumably results from oxidation of the intermediate lactol **24**, itself the product of initial oxidative cleavage of **22** to a dialdehyde; followed by cyclization.[24] The presence of the lactone was confirmed by IR spectroscopy: **24** displayed a C=O stretch at 1768 cm^{-1}, consistent with the presence of a 5-membered lactone.[25] The lactone was used without further purification. In order to retain the oxidation state of a carboxylic acid, while protecting against nucleophilic attack, we chose to transform the acid to the *tert*-butyl ester. Esterification of **24** with *tert*-butanol in the presence of 1,3-diisopropylcarbodiimide (DIC) and dimethylamino pyridine (DMAP)[26] afforded **26** in 60% yield from **23**. Addition of an aluminate, generated from the addition of benzylamine to a benzene solution of Me_3Al, into a solution of **26** afforded amidoalcohol **27** in 68% yield.[27] Oxidation of the resulting alcohol proceeded smoothly with Dess–Martin periodinane[28] to afford the ketone **28** in 54% yield. Deprotection of the *tert*-butyl ester was accomplished with refluxing catalytic *p*-toluenesulfonic acid (*p*-TsOH)[29] in benzene to give the corresponding acid. Esterification of the acid with (trimethylsilyl)diazomethane ($TMS-CH_2N_2$)[30] in benzene/methanol afforded **21** in 81% yield from **28**. The compound synthesized chemically from **23** matched the spectral properties of **21**, which was assigned to be the minor regioisomer from the nucleophilic opening of anhydride **18**. Therefore, we have created complimentary methods of desymmetrizing the cyclopentane ring system.

3. Conclusion

In conclusion, we have presented complimentary approaches to the regioselective functionalization of a [2.2.1] bicyclic system produced in a highly efficient and diastereoselective Diels–Alder reaction. Transmission of stereochemical information though the remainder of the ring system occurs either transiently (nucleophilic opening of an anhydride) or covalently (nucleophilic cleavage of a lactone). We are currently in the process of synthesizing scaffolds analogous to **12** and **13** using the chemistry disclosed herein.

4. Experimental

4.1. General

All non-aqueous reactions were conducted in flame dried glassware, under an atmosphere of N_2, and were stirred with a teflon coated magnetic stir-bar, unless otherwise stated. Air-sensitive reagents and solutions were transferred via syringe (unless otherwise stated) and were introduced to the reaction vessel through a rubber septum. Unless otherwise indicated, all procedures were carried out at ambient temperature (or room temperature, rt), which is approximately 23°C. Unless otherwise stated, temperatures other than rt denote the temperature of the cooling/heating bath. All distillations were performed under a N_2 atmosphere, or under reduced pressure using an aspirator (15–30 mm Hg), or vacuum pump (≈1 mm Hg). The term 'concentrated in vacuo' refers to removal of solvent by means of a Buchi rotary-evaporator attached to an aspirator pump (10 mm Hg). Purification by flash chromatography was performed following the procedure of Still[31] using the indicated solvent systems on EM Reagents silica gel 60 (230–400) mesh. Analytical thin layer chromatography (TLC) was performed using EM silica gel 60 F-254 precoated glass plates (0.25 mm). Visualization was effected by short-wave UV illumination and/or by dipping the plate into

a solution of $KMnO_4$,[32] or phosphomolybdic acid (PMA)[33] followed by heating on a hot plate.

Reagent-grade solvents were used without further purification for all extractions and work-up procedures. Double distilled water was used for all aqueous reactions, work-ups, and for the preparation of all aqueous solutions. Reaction solvents were dried and purified according to standard procedures by distillation under N_2 from an appropriate drying agent: tetrahydrofuran, diethyl ether, and benzene were distilled from sodium benzophenone ketyl; methylene chloride, diisopropylethyl amine, triethylamine, pyridine, acetonitrile, and toluene were distilled from calcium hydride. Cyclopentadiene was cracked at 140°C, and stored indefinitely at −80°C.

Proton nuclear magnetic resonance (NMR) spectra were obtained on a Bruker AMX-400 (400 MHz), or an Avance 400 (400 MHz) instrument. Carbon NMR spectra were obtained on an Avance 400 (75 MHz). Chemical shifts are reported in ppm (δ) relative to the appropriate deuterated solvent. Multiplicity was designated by the following abbreviations and combinations thereof: singlet (s), doublet (d), doublet of doublet (dd), doublet of triplets (dt), multiplet (m). Infrared (IR) spectra were recorded as thin films on KBr plates on a Perkin–Elmer 1610 FT-IR spectrophotometer calibrated with a polystyrene thin-film standard, and are reported in wavenumbers (cm^{-1}).

High resolution mass spectrometry (HRMS) was performed at the national mass spectrometry facility at the University of California, Riverside, California. Elemental analyses were obtained from Gailbraith Laboratories, Knoxville, Tennessee. Melting points were obtained using a Mel-Temp II capillary melting point apparatus and are uncorrected. The X-ray crystallographic data were collected on a standard Siemens SMART CCD Area Detector System equipped with a normal focus molybdenum-target X-ray tube operated at 2.0 kW (50 kV, 40 mA); further details of X-ray crystallographic analyses are presented in the supplementary material.

4.1.1. (±)-(2′R,3′R)-1-(3′-Isopropyl-bicyclo[2.2.1]hept-5-en-2-yl)-3-methyl-butan-1-one (7). 2,7-Dimethyloct-3-ene-5-one (compound **16**: 2.94 g, 19.11 mmol) was dissolved with 25 ml of dry CH_2Cl_2 to afford a 0.8 M solution. The resulting solution was cooled to 0°C for 10 min. Addition of Me_3Al (0.47 ml, 0.95 mmol, 2.0 M in hexanes) yielded slight gas evolution, which dissipated upon stirring at 0°C for an additional 10 min. To the yellow solution was added $AlCl_3$ (9.55 ml, 9.55 mmol, 1.0 M in CH_3NO_2) and the reaction was stirred an additional 5 min at 0°C. The reaction was cooled to −78°C for 10 min, at which point cyclopentadiene (12.61 g, 191.1 mmol, 5.0 M in CH_2Cl_2) was added. Upon addition of the diene, the reaction formed a thick white precipitate. The reaction was stirred at −78°C for 2 h. After quenching with pyridine (10 ml, 125 mmol), the reaction was quickly warmed to rt. The resulting thick white slurry was filtered through silica (250 ml), and washed with Et_2O (4×60 ml). The organics were reduced in vacuo. Azeotropic removal of the pyridine and CH_3NO_2 was effected by treatment with heptane (4×50 ml) affording a yellow residue. Purification via flash chromatography (silica, 95:5, hexanes/Et_2O) afforded **7** as a yellow oil (3.78 g, 90% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 6.35 (1H, dd, J=4, 6 Hz); 5.92 (1H, dd, J=3, 6 Hz); 3.56 (1H, bs); 3.21 (1H, bs); 3.06 (1H, t, J=5 Hz); 2.80–2.86 (2H, m); 2.66–2.69 (1H, m); 2.09–2.16 (2H, m); 1.94–2.01 (2H, m); 1.61 (3H, d, J=7 Hz); 1.54 (6H, t, J=7 Hz); 1.48 (3H, d, J=7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.4, 139.3, 131.6, 58.3, 51.0, 48.5, 47.1, 46.7, 45.2, 32.7, 24.3, 22.7, 22.5, 22.2, 21.8. FT-IR (thin film, from $CDCl_3$): 3026, 1702, 909, 650 cm^{-1}. HRMS calcd for $C_{15}H_{24}O$ (M+) 220.1827, found 220.1839.

4.1.2. (±)-(1*S*,3*R*,4*R*,5*R*)-4-Isopropyl-5-(3-methyl-butyryl)-cyclopentane-1,3-dicarboxylic acid (17). Diels–Alder adduct **7** (3.03 g, 13.77 mmol) was dissolved in CH_2Cl_2 (125 ml) and cooled to −78°C for 30 min. Ozone (O_3) was bubbled into the solution until the reaction attained a blue color (20 min), then for an additional 30 min. O_2 was then bubbled through the system to remove excess O_3. After the blue color had dissipated, the reaction was warmed to 0°C for 15 min. The reaction was quenched portionwise with triphenylphosphine (PPh_3, 4.35 g, 16.35 mmol). After addition of PPh_3 was complete, the reaction was stirred for 1 h at 0°C, or until starch paper revealed that all of the peroxides had been consumed. Reaction contents were reduced in vacuo and carried on crude. The crude dialdehyde was dissolved in 70 ml of an 80:20 *tert*-butanol/2-methyl-2-butene solution at rt. $NaClO_2$ (22.6 g, 250.6 mmol), and $NaH_2PO_4{\cdot}H_2O$ (26.60, 192.7 mmol) were dissolved into 225 ml of H_2O. The resulting solution was added via an addition funnel to the aldehyde solution over 1 h. The reaction was stirred for 18 h at rt, then rendered basic with saturated aqueous (sat. aq.) Na_2CO_3, and extracted with 5×100 ml of Et_2O. The aqueous layer was carefully acidified to a pH=3 with an aqueous buffered solution of $NaH_2PO_4{\cdot}H_2O$/concentrated HCl (pH=2–3). The resulting aqueous suspension was extracted sequentially with 6×100 ml of EtOAc, followed by 5×100 ml of CH_2Cl_2. The combined EtOAc and CH_2Cl_2 washes were dried over Na_2SO_4, filtered, and reduced in vacuo to afford a white solid. Recrystallization of the crude diacid from benzene afforded **17** as a white solid (2.94 g, 75% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 3.08 (1H, bs); 2.90–2.97 (1H, m); 2.67–2.74 (1H, m); 2.4–2.5 (2H, m); 2.37 (1H, d, J=6 Hz); 2.29–2.34 (2H, m); 2.16 (1H, septet, J=6 Hz); 1.79 (1H, septet, J=6 Hz); 0.98 (6H, dd, J=8 Hz, J=10 Hz); 0.91 (6H, d, J=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): d 210.3, 180.8, 179.0, 55.0, 50.7, 50.6, 47.0, 46.2, 32.4, 32.3, 24.0, 22.5, 22.4, 20.2, 19.8. FT-IR (thin film, from $CDCl_3$) 3557, 2959, 1710 cm^{-1}. HRMS calcd for $C_{15}H_{28}NO_5$ ($M+NH_4^+$) 302.1967 found 302.1980. Mp: 110–112°C.

4.1.3. A representative synthesis of amides 20 and 21 as presented in Table 1. Entry 5 is shown below. The diacid **17** (114.3 mg, 0.403 mmol) was dissolved to yield an 0.7 M solution in CH_2Cl_2. To the colorless, homogeneous solution was added DCC (82.9 mg, 0.402 mmol) at rt. Upon addition of DCC to the reaction, an immediate white precipitate formed. The reaction was allowed to stir for 5 h at rt, then filtered through Celite. The Celite pad was washed with CH_2Cl_2 (5×2 ml). The combined organics were reduced in vacuo to afford a white solid, which was used without

further purification. The crude anhydride was dissolved in CH_2Cl_2/CH_3CN 9:1 to yield an 0.3 M solution. $MgCl_2$ (45.93 mg, 0.48 mmol) was added to the solution and stirred for 10 min at rt. The amine was added dropwise via syringe. After allowing the reaction to stir for 18 h at rt, it was quenched with a 10% HCl solution to a pH=1. Extraction with CH_2Cl_2, followed by drying over Na_2SO_4, filtering and reduction of the volume in vacuo afforded a yellow residue. The residue was dissolved into 28% methanolic benzene to provide a 0.11 M solution. Dropwise addition of TMS–CH_2N_2 resulted in vigorous gas evolution. After stirring for 2 h, the reaction was filtered through silica, eluted with EtOAc, and reduced in vacuo to afford a yellow oil. Crude ^{1}H NMR of the reaction mixture revealed that the opening of the anhydride occurred with 5.3/1 selectivity **20**:**21**. The reaction was purified via flash chromatography (silica, 75:25, hexanes/ethyl acetate) which afforded **20** and **21** in a combined yield of 99 mg (64%).

(±)-(1S,2R,3R,4R)-4-Benzylcarbamoyl-3-isopropyl-2-(3-methyl-butyryl)-cyclopentanecarboxylic acid methyl ester (**20**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.37 (5H, m); 4.76 (1H, d, J=15 Hz); 4.59 (1H, d, J=15 Hz); 4.53 (1H, d, J=10 Hz); 3.63 (3H, s); 3.20–3.24 (1H, m); 3.11–3.16 (1H, m) 2.83 (1H, m); 2.59 (1H, dt, J=3, 13 Hz); 2.40–2.49 (2H, m); 2.29–2.30 (1H, m); 1.92–1.98 (1H, m); 0.97–1.02 (10H, m); 0.94 (3H, d, J=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8, 175.6, 140.1, 136.3, 128.2, 127.1, 126.9, 111.5, 56.7, 51.7, 46.2, 44.7, 44.4, 43.9, 31.9, 30.4, 26.9, 23.9, 23.7, 21.9, 17.2. FT-IR (thin film, from $CDCl_3$): 3051, 1731, 1709, 1668 cm^{-1}. Elemental Analysis: calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61; found C, 71.10; H, 8.14; N, 3.72.

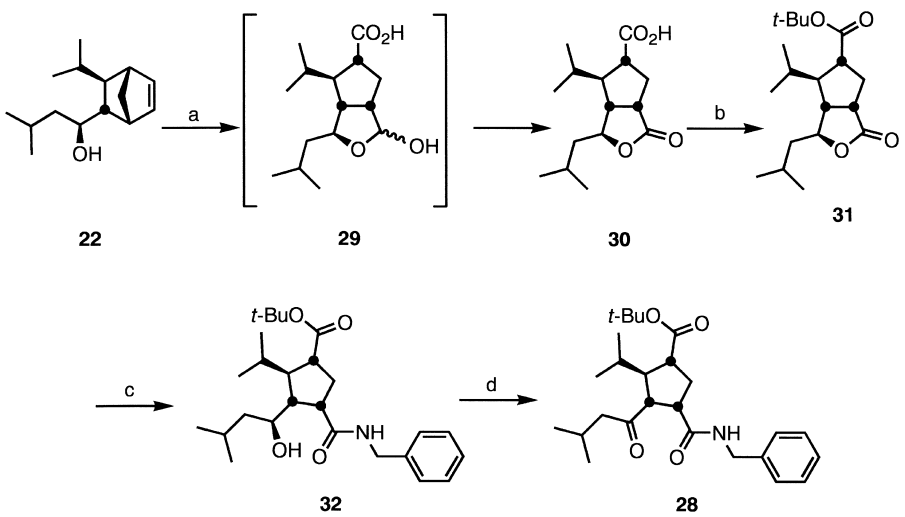
(±)-(1R,2R,3R,4S)-4-Benzylcarbamoyl-2-isopropyl-3-(3-methyl-butyryl)-cyclopentanecarboxylic acid methyl ester (**21**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.27 (5H, m); 6.63 (1H, bs); 4.43–4.47 (2H, m); 3.64 (3H, s); 3.14 (1H, dd, J=4, 8 Hz); 2.90–2.92 (1H, m); 2.61 (1H, apparent q, J=6 Hz); 2.32–2.45 (5H, m); 2.12 (1H, septet, J=6 Hz); 1.75 (1H, sextet, J=6 Hz); 0.96 (6H, dd, J=7, 4 Hz); 0.91 (6H, dd, J=1, 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.2, 174.8, 173.3, 138.6, 128.6, 127.6, 127.3, 55.24, 52.3, 51.9, 51.8, 49.2, 47.8, 43.5, 33.71, 32.2, 24.0, 22.6, 22.5, 20.3, 19.9. FT-IR (thin film, from $CDCl_3$): 3315, 1730, 1718, 1709 cm^{-1}. HRMS: calcd $C_{23}H_{33}NO_4$ (M+) 387.2410, found 387.2424. Elemental Analysis: calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61. Found C, 71.67; H, 8.73; N, 3.87. Mp: 95–96°C.

4.1.4. A representative synthesis of alcohols 22 and 23 as presented in Table 2. Entry 4 is shown below. Ketone **7** (75.7 mg, 0.34 mmol) was dissolved to a concentration of 0.5 M in THF. After cooling the solution to −78°C for 15 min, L-selectride (0.71 ml, 0.71 mmol, 1.0 M solution in THF) was added via syringe. After stirring at 1 h at −78°C, TLC analysis of the reaction showed only SM (starting material). The reaction was warmed to 0°C over 4 h, at which point TLC showed complete consumption of SM. Reaction was quenched sequentially with 0.7 ml of 15% aq. NaOH, then 0.7 ml of 30% aq. H_2O_2. The reaction mixture was extracted with CH_2Cl_2 (3×5 ml). The organic extracts were pooled, dried over Na_2SO_4, filtered, and reduced in vacuo to give an oil that crystallized upon standing. The residue was purified via flash chromatography (silica, 88:12 hexanes/Et_2O) to give 55 mg (72%) of both **22** and **23** in a 2.4:1 ratio.

(±)-(1S,1′R,3′S)-1-(3′-Isopropyl-bicyclo[2.2.1]hept-5-en-2-yl)-3-methyl-butan-1-ol (**22**). ^{1}H NMR (400 NMR, $CDCl_3$): δ 6.23 (1H, bs); 6.16 (1H, bs); 3.43 (1H, m); 2.92 (1H,bs); 2.70 (1H, bs); 1.77–1.83 (1H, m); 1.72–1.77 (1H, m); 1.53–1.58 (2H, m); 1.37–1.45 (2H, m); 1.32–1.35 (1H, d, J=8 Hz); 1.21–1.25 (1H, m); 0.99 (6H, dd, J=7, 9 Hz); 0.94 (3H, d, J=6 Hz); 0.88 (3H, d, J=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 134.3, 72.5, 50.5, 49.0, 47.1, 46.4, 44.6, 43.6, 32.6, 24.7, 23.8, 22.4, 21.8, 21.4. FT-IR (thin film, from $CDCl_3$): 3500, 2950 cm^{-1}. HRMS calcd for $C_{15}H_{26}O$ (M+) 222.1983 found 222.1982.

(±)-(1R,1′R,3′S)-1-(3′-Isopropyl-bicyclo[2.2.1]hept-5-en-2-yl)-3-methyl-butan-1-ol (**23**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.19 (1H, bs); 3.00–3.06 (1H, m); 2.71 (2H, bs); 1.81 (1H, septet, J=6 Hz); 1.63–1.67 (1H, m); 1.50 (1H, m); 1.43 (1H, d, J=8 Hz); 1.30–1.35 (4H, m); 1.25 (1H, m); 1.01 (3H, d, J=7 Hz); 0.96 (3H, d, J=7 Hz); 0.92 (3H, d, J=7 Hz); 0.85 (3H, d, J=7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 133.8, 51.7, 50.3, 46.5, 45.6, 45.1, 44.9, 32.6, 24.2, 22.8, 21.5, 21.3. FT-IR (thin film, from $CDCl_3$): 3470, 2956, 1466 cm^{-1}. HRMS calcd $C_{15}H_{26}O$ (M+) 222.1983 found 222.1982.

4.1.5. (±)-(1*aS*,3*R*,3*aR*,4*R*,5*R*)-3-Isobutyl-4-isopropyl-1-oxo-hexahydro-cyclopenta[*c*]furan-5-carboxylic acid *tert*-butyl ester (26). Alcohol **23** (1.00 g, 4.50 mmol) was dissolved to a concentration of 0.11 M in 2/2/3 $CH_3CN/CCl_4/H_2O$. Addition of $NaIO_4$ (5.76 g, 27.0 mmol), and $RuCl_3{\cdot}H_2O$ (18 mg, 0.09 mmol) caused formation of a white precipitate. The reaction was stirred for 8 h at rt, then quenched sequentially with water (2 ml) and aq. 10% HCl until a pH=1 was reached. The aqueous layer was extracted with CH_2Cl_2 (4×15 ml), and filtered through Celite. The filtrate was reduced in vacuo, to afford a purple solid, which was used without further purification. The crude acid was dissolved to a concentration of 0.6 M in CH_2Cl_2, and cooled to 0°C. To the purple solution, sequential addition of *tert*-butanol (0.50 ml, 6.75 mmol), DMAP (0.11 g, 0.90 mmol), and DIC (0.99 ml, 6.3 mmol) resulted in formation of a precipitate. After the stirring the reaction at rt for 24 h, it was quenched with water (2 ml) and 10% aq. HCl solution until a pH=1 was reached. Extraction of the resulting mixture with CH_2Cl_2, followed by drying the organics over Na_2SO_4, filtering, and reduction of the solvent in vacuo yielded a purple oil. Purification of this oil via flash chromatography (silica, 75:25 hexanes/ethyl acetate) afforded **25** as a white solid (0.87 g, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.61–4.65 (1H, m); 3.05–3.10 (1H, m); 2.60–2.72 (2H, m); 2.51 (1H, apparent q, J=1, 7 Hz); 2.18–2.31 (2H, m); 1.67–1.91 (3H, m); 1.44 (9H, s); 1.31–1.37 (1H, m); 0.87–0.99 (12H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.1, 174.3, 80.9, 79.6, 48.0, 48.0, 47.7, 47.1, 40.6, 33.1, 32.6, 31.1, 27.8, 25.5, 23.6, 21.6, 21.3, 17.8. FT-IR (thin film, from $CDCl_3$): 2959, 1767, 1718, 1467, 1368, 1152 cm^{-1}. HRMS calcd $C_{19}H_{36}NO_4$ ($M+NH_4^+$) 342.2644 found 342.2654.



Scheme 5. This scheme details the transformation of alcohol **22** to **28**, via an analogous series of reactions to that shown in Scheme 4. (a) $RuCl_3{\cdot}H_2O$, $NaIO_4$, 2/2/3 $CCl_4/CH_3CN/H_2O$, rt; (b) DIC, DMAP, *tert*-butanol, CH_2Cl_2, rt (59% yield from **22**); (c) (i) $(CH_3)_3Al$, benzylamine, benzene, rt, (ii) **31**, benzene, 40°C (45% yield); (d) Dess–Martin periodinane, CH_2Cl_2, rt (71% yield).

4.1.6. (±)-(1*R*,1′*R*,2*R*,3*R*,4*S*)-4-Benzylcarbamoyl-3-(1′-hydroxy-3′-methyl-butyl)-2-isopropyl-cyclopentanecarboxylic acid *tert*-butyl ester (27). Benzyl amine (0.22 ml, 2.0 mmol) was dissolved in 5.0 ml of benzene at rt. Me_3Al (1.0 ml, 2.0 mmol, 2.0 M in hexanes) was added dropwise, via a syringe, to the benzene solution. The reaction was stirred at vortex speeds for 15 min. Concurrently, **6** (40.0 mg, 0.13 mmol) was dissolved in 0.1 ml of benzene at rt. The aluminate of benzyl amine (0.79 ml, 0.32 mmol, 0.4 M in benzene) was added dropwise, via syringe, to the benzene solution of **6**. The reaction was immediately warmed to 50°C, and stirred at this temperature for 5 h. It was then cooled to rt, and immediately quenched with 10% aq. HCl until a pH=1 was reached. Extraction of the resulting aqueous solution with CH_2Cl_2 (5×5 ml), drying the organics over Na_2SO_4, subsequent filtering, and reduction of the solvent in vacuo afforded an off-white solid. Purification of the solid via flash chromatography (silica, 75:25 hexanes/ethyl acetate) yielded **7** as a white solid (37 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.34 (5H, m); 6.65 (1H, m); 4.47–4.50 (2H, m); 3.75–3.79 (1H, m); 2.98 (1H, bs); 2.75–2.79 (1H, m); 2.43–2.52 (2H, m); 2.27 (1H, q, J=13 Hz); 2.13–2.17 (1H, m); 2.03–2.06 (1H, m); 1.65–1.74 (2H, m); 1.44 (10H, s); 0.87–0.92 (6H, m); 0.82 (6H, apparent d, J=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.3, 173.6,138.2, 128.7, 127.9, 127.5, 80.6, 70.4, 51.3, 50.3, 47.8, 46.3, 44.1, 43.6, 35.6, 32.0, 28.0, 24.5, 23.6, 21.9, 21.3, 18.3. FT-IR (thin film, from $CDCl_3$): 3288, 3055, 2956, 1721, 1640, 1521, 1367, 704 cm^{-1}. HRMS calcd $C_{26}H_{42}NO_4$ (M+H) 432.3113 found 432.3131.

4.1.7. (±)-(1*R*,2*R*,3*R*,4*S*)-4-Benzylcarbamoyl-2-isopropyl-3-(3-methyl-butyryl)-cyclopentanecarboxylic acid *tert*-butyl ester (28). Dess–Martin periodinane (42 mg, 0.10 mmol) was slurried into 0.3 ml of CH_2Cl_2 at rt. To this solution, alcohol **27** (22.5 mg, 0.05 mmol) in 0.2 ml of CH_2Cl_2 was added providing a clear, colorless solution. After the reaction stirred for 1 h, TLC showed consumption of starting material. The reaction was quenched with saturated aq. Na_2CO_3 until a pH=10 was reached. The aqueous layer was extracted with CH_2Cl_2 (5×2 ml). The organics were combined, dried over Na_2SO_4, filtered, and reduction of solvent in vacuo afforded a white solid. Purification of the resulting solid via flash chromatography (silica, 80:20 hexanes/ethyl acetate) yielded **28** as a white solid (12 mg, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.33 (5H, m); 6.15 (1H, bs); 4.3–4.48 (2H, m); 3.19 (1H, dd, J=5, 8 Hz); 2.88–2.91 (1H, m); 2.55–2.60 (1H, m); 2.45–2.5 (1H, m); 2.3–2.41 (3H, m); 2.12–2.20 (2H, m); 1.72–1.77 (1H, m); 1.42 (9H, s); 0.89–0.97 (12H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.4, 174.2, 172.0, 152.2, 128.6, 127.9, 127.4, 80.7, 55.4, 51.8, 51.0, 49.7, 48, 43.7, 32.9, 32.0, 28.0, 23.8, 22.6, 22.5, 20.5, 19.8. FT-IR (thin film, from $CDCl_3$): 3365, 2955, 1719, 1703, 1650, 1517, 1366, 1159 cm^{-1}. HRMS calcd $C_{26}H_{40}NO_4$ 430.2957 (M+H) found 430.2957 (Scheme 5).

4.1.8. (±)-(1a*S*,3*S*,3a*R*,4*R*,5*R*)-3-Isobutyl-4-isopropyl-1-oxo-hexahydro-cyclopenta[*c*]furan-5-carboxylic acid *tert*-butyl ester (31). Alcohol **22** (0.52 g, 2.35 mmol) was dissolved in 2/2/3 $CH_3CN/CCl_4/H_2O$ to yield a 0.11 M solution. Addition of $NaIO_4$ (3.0 g, 14.1 mmol), and $RuCl_3{\cdot}H_2O$ (9.7 mg, 0.05 mmol) caused formation of a white precipitate. The reaction was allowed to stir for 8 h at rt, then quenched sequentially with water (2 ml) and aq. 10% HCl solution until the pH=1. The aqueous layer was extracted with CH_2Cl_2 (4×15 ml), and filtered through Celite. The filtrate was reduced in vacuo to afford a purple solid, which was used without further purification. The crude acid was dissolved in CH_2Cl_2 to yield a 0.6 M solution, and cooled to 0°C for 10 min. To the purple solution, sequential addition of *tert*-butanol (0.33 ml, 3.53 mmol), DMAP (57 mg, 0.47 mmol), and DIC (0.52 ml, 3.29 mmol) resulted in formation of a precipitate. After the reaction stirred at rt for 24 h, it was quenched with water (2 ml), and then 10% aq. HCl was added until the pH=1. Extraction of the mixture with CH_2Cl_2, followed by drying the organics over Na_2SO_4, filtering, and reduction of the solvent in vacuo yielded a purple oil. Purification of this oil via flash chromatography (silica, 75:25 hexanes/ethyl acetate) afforded **31** as a white solid (0.45 g, 59% yield). ^{1}H

NMR (400 MHz, $CDCl_3$): δ 4.37–4.41 (1H, m); 3.01–3.07 (1H, m); 2.4–2.67 (1H, m); 2.29–2.39 (2H, m); 2.10–2.20 (2H, m); 1.81–1.86 (1H, m); 1.67–1.72 (1H, m); 1.54–1.61 (1H, m); 1.44 (9H, s); 1.41 (1H, m); 0.92–0.96 (12H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.2, 173.9, 83.5, 80.9, 55.4, 50.3, 50.1, 45.4, 44.6, 33.2, 31.1, 27.9, 24.7, 23.3, 21.6, 20.3, 20.3. FT-IR (thin film, from $CDCl_3$): 2960, 2872, 1764, 1725, 1467, 1368, cm^{-1}. HRMS calcd $C_{19}H_{33}O_4$ (M+H) 325.2379 found 325.2365.

4.1.9. (±)-(1*R*,1′*S*,2*R*,3*R*,4*S*)-4-Benzylcarbamoyl-3-(1′-hydroxy-3-methyl-butyl)-2-isopropyl-cyclopentanecarboxylic acid *tert*-butyl ester (32). Benzylamine (0.22 ml, 2.0 mmol) was dissolved in 5.0 ml of benzene at rt. Me_3Al (1.0 ml, 2.0 mmol, 2.0 M in hexanes) was added dropwise via a syringe to the benzene solution. The reaction was stirred rapidly for 15 min. Concurrently, **31** (0.43 g, 1.39 mmol) was dissolved in benzene to provide a 0.5 M solution. The aluminate of benzyl amine (3.49 ml, 3.49 mmol, 0.4 M in benzene) was added dropwise, via syringe, to the benzene solution of **31**. The reaction was immediately warmed to 50°C, and stirred at this temperature for 5 h. The reaction was then cooled to rt, and immediately quenched with 10% aq. solution of HCl until a pH=1 was reached. Extraction of the resulting aqueous solution with CH_2Cl_2 (5×5 ml), drying the organics over Na_2SO_4, subsequent filtering, and reduction of the solvent in vacuo afforded a yellow oil. Purification of this oil via flash chromatography (silica, 75:25 hexanes/ethyl acetate) yielded **32** as a yellow oil (270 mg, 45% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.27–7.34 (5H, m); 6.96 (1H, t, *J*=5 Hz); 4.40–4.50 (2 h, m); 3.69 (2H, bs); 2.73 (1H, q, *J*=8 Hz); 2.45–2.52 (1H, m); 2.36–2.41 (1H, m); 2.16–2.38 (1H, m); 2.05–2.12 (1H, m); 1.95 (1H, dt, *J*=8, 16 Hz); 1.78–1.85 (2H, m); 1.51–1.57 (1H, m); 1.49 (9H, s); 1.28–1.29 (1H, m); 0.87–0.96 (12H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 176.0, 137.9, 128.7, 128.0, 127.5, 80.7, 70.3, 52.1, 51.1, 48.1, 45.8, 45.1, 44.0, 34.1, 29.7, 24.9, 23.6, 21.9, 21.3, 17.8. FT-IR (thin film, from $CDCl_3$): 3290, 2956, 1721, 1638, 1548, 1454, 1367, 1150, 908, 734 cm^{-1}. HRMS calcd $C_{26}H_{42}NO_4$ (M+H) 432.3113 found 432.3129.

4.1.10. (±)-(1*R*,2*R*,3*R*,4*S*)-4-Benzylcarbamoyl-2-isopropyl-3-(3-methyl-butyryl)-cyclopentanecarboxylic acid *tert*-butyl ester (28, from 32). Dess–Martin periodinane (0.35 g, 0.83 mmol) was slurried into 2.1 ml of CH_2Cl_2 at rt. To this solution, alcohol **32** (0.24 g, 0.55 mmol) in 2.5 ml of CH_2Cl_2 was added at rt. The reaction immediately cleared upon addition of **32**. After the reaction stirred for 1 h, TLC showed consumption of starting material. The reaction was quenched with saturated aq. Na_2CO_3 until a pH=10 was reached. The aqueous mixture was extracted with CH_2Cl_2 (4×10 ml). The organics were combined, dried over Na_2SO_4, filtered, and reduced in vacuo to afford a white solid. Purification of this solid via flash chromatography (silica, 80:20 hexanes/ethyl acetate) yielded **28** as a white solid (167 mg, 71% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.33 (5H, m); 6.15 (1H, bs); 4.3–4.48 (2H, m); 3.19 (1H, dd, *J*=5, 8 Hz); 2.88–2.91 (1H, m); 2.55–2.60 (1H, m); 2.45–2.5 (1H, m); 2.3–2.41 (3H, m); 2.12–2.20 (2H, m); 1.72–1.77 (1H, m); 1.42 (9H, s); 0.89–0.97 (12H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.4, 174.2, 172.0, 152.2, 128.6, 127.9, 127.4, 80.7, 55.4, 51.8, 51.0, 49.7, 48, 43.7, 32.9, 32.0, 28.0, 23.8, 22.6, 22.5, 20.5, 19.8. FT-IR (thin film, from $CDCl_3$): 3365, 2955, 1719, 1703, 1650, 1517, 1366, 1159 cm^{-1}. HRMS calcd $C_{26}H_{40}NO_4$ 430.2957 (M+H) found 430.2957.

4.1.11. (±)-(1*R*,2*R*,3*R*,4*S*)-4-Benzylcarbamoyl-2-isopropyl-3-(3-methyl-butyryl)-cyclopentanecarboxylic acid methyl ester (21). Ester **28** (76 mg, 0.18 mmol) was dissolved in 2.0 ml of benzene at rt. *p*-TsOH·H_2O (3.36 mg, 0.018 mmol) was then added, and the solution heated to reflux. After heating at reflux for 2 h, TLC indicated consumption of starting material. The reaction was allowed to cool to rt, contents were reduced in vacuo, and used without further purification. The crude acid was dissolved in 28% methanolic benzene to provide a 0.11 M solution. TMS–CH_2N_2 (0.35 ml, 0.71 mmol) was added dropwise via syringe, resulting in vigorous gas evolution. After stirring for 2 h at rt, the reaction contents were reduced in vacuo. Purification of the resulting residue via flash chromatography (silica, 75:25 hexanes/ethyl acetate) afforded a colorless oil (55 mg, 81% yield). The spectral characteristics matched the minor product isolated from the nucleophilic opening of anhydride **18**. ^1H NMR (400 MHz, $CDCl_3$): δ 7.27–7.37 (5H, m); 4.76 (1H, d, *J*=15 Hz); 4.59 (1H, d, *J*=15 Hz); 4.53 (1H, d, *J*=10 Hz); 3.63 (3H, s); 3.20–3.24 (1H, m); 3.11–3.16 (1H, m) 2.83 (1H, m); 2.59 (1H, dt, *J*=3, 13 Hz); 2.40–2.49 (2H, m); 2.29–2.30 (1H, m); 1.92–1.98 (1H, m); 0.97–1.02 (10H, m); 0.94 (3H, d, *J*=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8, 175.6, 140.1, 136.3, 128.2, 127.1, 126.9, 111.5, 56.7, 51.7, 46.2, 44.7, 44.4, 43.9, 31.9, 30.4, 26.9, 23.9, 23.7, 21.9, 17.2. FT-IR (thin film, from $CDCl_3$): 3051, 1731, 1709, 1668 cm^{-1}. Elemental Analysis: calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61. Found C, 71.10; H, 8.14; N, 3.72.

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