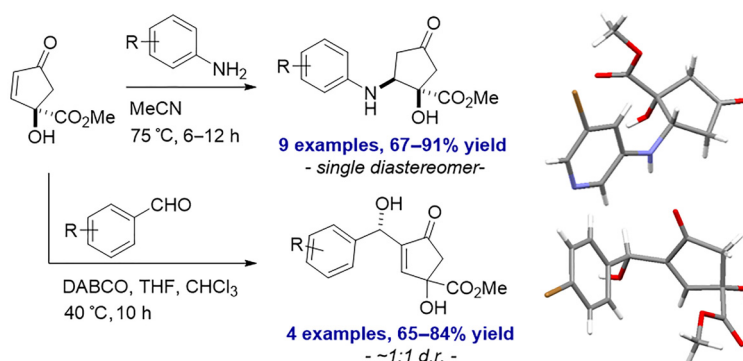M. Baumann et al.

Diastereoselective Synthesis and Diversification of Highly Functionalized Cyclopentanones

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Abstract An efficient entry into highly substituted cyclopentanones is presented based on functionalizing cyclopentenones by means of an aza-Michael reaction with different aniline nucleophiles. The excellent diastereoselectivity of this process is ascribed to H-bonding between a tertiary alcohol and the incoming nucleophiles. Additionally, the functionalization of the parent cyclopentenones via the Baylis–Hillman reaction is demonstrated. Together, these transformations showcase the elaboration of a simple precursor by installation of versatile functionalities at either the α- or β-position of the embedded enone and thus represent valuable methods for the construction of diversely functionalized cyclopentanones.

The efficient assembly of suitably functionalized three-dimensional building blocks has in recent years gained increasing interest as it allows for the generation of structures occupying new chemical and biological space.[1] Moreover, the sustainability of such processes is of increasing importance being a key feature that enables the reliable and future-proofed construction of such chiral building blocks.[2] Together with the operational simplicity and robustness modern synthesis efforts aim to adhere to green chemistry principles whenever possible.[3] In a recent synthesis program, we have, for instance, developed a flow process for converting bioderived D-glucono-1,5-lactone (**1**) into chiral cyclopentenone **4** in continuous mode (Scheme 1).[4]

Highlights of this work included the application of powder dosing equipment and counter-current extraction modules allowing for the continuous production of **4** and selected key intermediates on large scale (>100 g). Furthermore, the successful implication of this route avoided the

Scheme 1 Continuous flow synthesis of cyclopentenone **4**
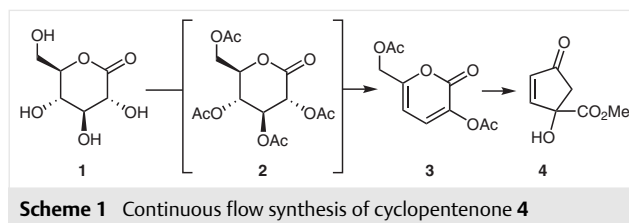
use of excessive or hazardous solvents and reagents as well as the need for chromatographic purifications. With a robust route to cyclopentenone **4** in hand we subsequently wished to study its conversion into further products of interest, especially those decorated with pendant amine functionalities. Crucially, we envisaged such aminohydroxy-cyclopentanones to be worthwhile targets as related structures such as (–)-agelastatin A (**5**), pactamycin (**6**), or peramivir (**7**) are known to possess interesting biological properties. In addition, as highly efficient and modern routes towards such structures have been developed recently,[5] providing a rapid access to simplified derivatives is becoming equally desirable (Figure 1).

Figure 1 Structures of bioactive cyclopentanes
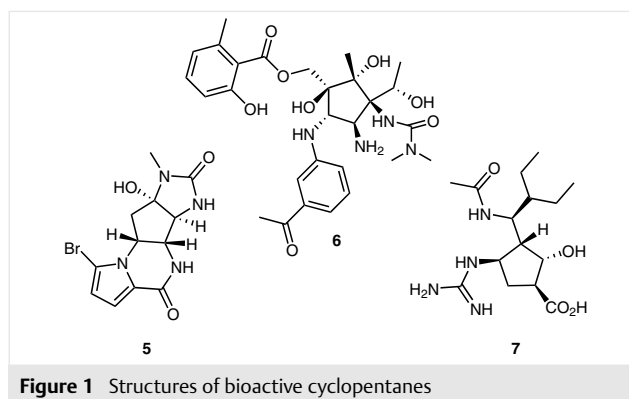
We commenced our study by investigating the conjugate addition of different anilines **8** to cyclopentenone **4**. Screening different solvents it was found that polar, aprotic solvents such as MeCN, 1,4-dioxane or DMF were preferred over nonpolar solvents (dichloromethane, toluene, hexanes), especially when high concentrations of 2–4 M were employed. We thus opted for MeCN as a suitable and benign solvent and subsequently studied the effect of different temperatures keeping the concentration at 3 M throughout. It was quickly established that temperatures of 50–75 °C gave full conversion within 6–12 hours whereas lower temperatures significantly slowed down the reaction. We therefore identified the ideal conditions to be the use of MeCN with high concentration of both substrates (**4** and **8**, 1:1 ratio, 3 M) at a reaction temperature of 70 °C (Scheme 2).
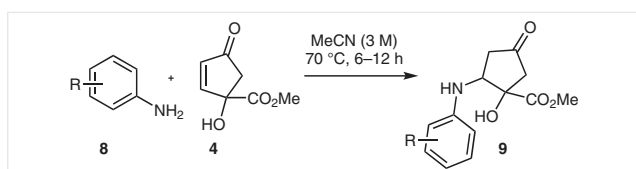
Scheme 2 Optimized conditions for preparing aniline adducts

With these conditions in hand, the reaction of a series of anilines with substrate **4** was next investigated aiming to establish the generality of this approach. We were thus pleased to see the smooth reaction of a variety of anilines under the established reaction conditions. As expected, electron-rich anilines gave faster reactions than neutral systems, whereas electron-poor anilines (R = 4-CN, 3-NO$_2$) gave very low conversion (~10%) to the desired product after 12–24 hours. It was also found that secondary anilines (R = H, *N*-methyl, or *N*-benzyl) were poor reaction partners due to steric hindrance, typically resulting in low conversion only (5–10% after 24 h). Importantly, a variety of different substitution patterns on the arene moiety of primary anilines was tolerated allowing for the creation of diversely functionalized systems. In addition, heteroaryl amines such as those based on pyridines, as well as biaryl amines are well tolerated in this transformation furnishing the desired adducts in good to excellent isolated yields and as a single diastereoisomer after purification via column chromatography (Scheme 3).

Crucially, these products were obtained as single diastereomers prompting us to investigate the origin of this stereoselectivity. We therefore crystallized products **9e** and **9g** allowing for single crystal diffraction experiments to be performed. These structures both indicate a *syn*-relationship between the tertiary alcohol and the amine functionality (Figure 2).[6]

We reasoned that this diastereoselectivity is the result of hydrogen bonding where the hydroxyl group directs the incoming amine nucleophile in a *syn*-fashion (see Scheme 3). It appears that this hydrogen bonding is not disturbed by additional hydrogen bond acceptors such as the pyridine nitrogen as evidenced in structure **9g**.

Biographical Sketches

Marcus Baumann graduated from Philipps University Marburg (Germany) in 2007 and subsequently undertook Ph.D. studies with Prof. Steven V. Ley at the University of Cambridge (UK) focusing on developing continuous flow processes for key organic transformations and natural product applications. In 2011, he was awarded a Feodor Lynen fellowship from the Alexander-von-Humboldt foundation allowing him to work with Prof. Larry E. Overman at the University of California Irvine (U.S.A.). Upon completion of this postdoctoral fellowship, he returned to the UK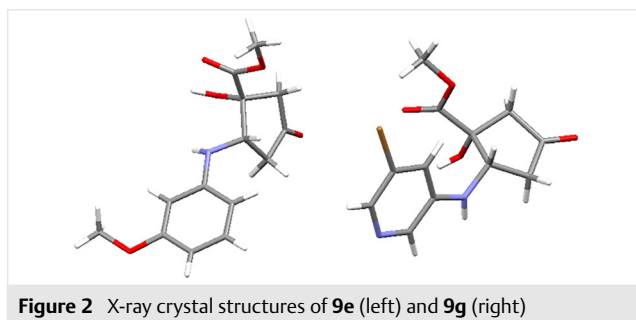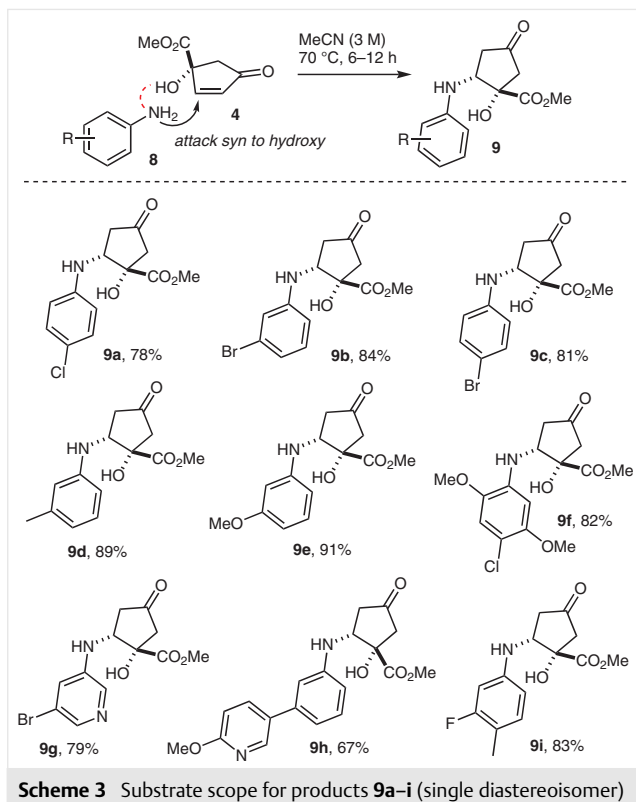 to join Prof. Ian R. Baxendale at Durham University as a senior postdoctoral research associate where his research interests lied in the area of continuous flow approaches applied to the synthesis of various bioactive entities. In 2017, he joined University College Dublin as an Assistant Professor in Continuous Flow Chemistry.

Ian R. Baxendale obtained his Ph.D. under the supervision of Prof. Pavel Kocovsky at the University of Leicester. He then moved to a postdoctoral position with Prof. Steven V. Ley at the University of Cambridge, initially conducting natural product synthesis before moving into the area of solid-supported reagents and scavengers. In 2008, he was promoted to Senior Research Associate in the Department of Chemistry and then in 2009 was awarded a Royal Society University Research Fellowship, becoming a member of the faculty. In 2012, he moved to Durham to take up the Chair of Synthetic Chemistry. His research interests are the design and implementation of new enabling technologies such as flow chemical synthesis (FCS), synthesis automation methodologies (SAM), microwave reactors, and immobilized reagents and scavengers to expedite complex chemical syntheses.

Scheme 3 Substrate scope for products **9a–i** (single diastereoisomer)

Figure 2 X-ray crystal structures of **9e** (left) and **9g** (right)

Having accomplished the efficient functionalization of the β-position of the cyclopentenone building block **4**, we furthermore wished to establish whether the adjacent α-position is amenable to effective derivatization. To this end, the reaction of **4** was exploited with a small selection of benzaldehydes **10** via a Baylis–Hillman reaction. After screening different solvents, it was found that a mixture of chloroform and THF (1:1 v/v, 1.5 M) worked best in combination with DABCO as a catalyst (25 mol%) to give the desired reaction products **11** (Scheme 4). Using ^{1}H NMR as a reliable technique to establish reaction progress allowed the identification of suitable conditions that promoted full conversion of all substrates within 10 hours at 40 °C.

Furthermore, we noticed that under the chosen reaction conditions cyclopentenone **4** is a fluctional species that undergoes additional transformations such as the formation

Scheme 4 Baylis–Hillman reaction of **4** and benzaldehydes **10**
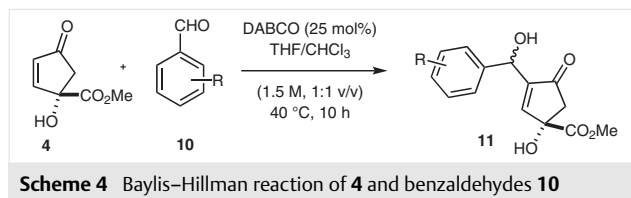
of the rearrangement structure **4c** (isolable yield 50–60%), which likely results from an allylic transposition reaction of **4** via intermediate **4b** (Scheme 5).

Scheme 5 Reaction pathways of cyclopentenone **4**
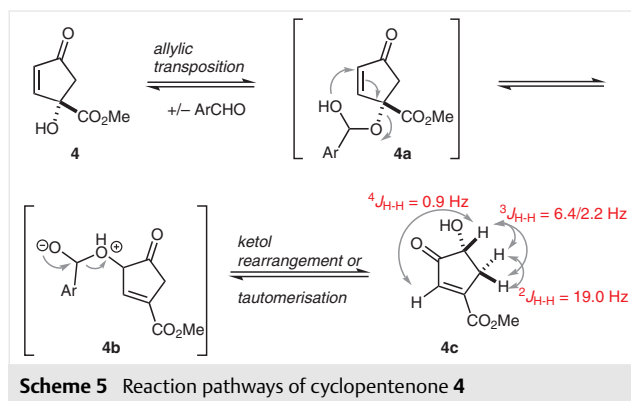
This material **4c** was identified based on a combination of ^{1}H NMR and ^{13}C NMR techniques and did not form unless all components were present in the reaction mixture (**4**, **10**, and DABCO). Based on this, we suggest a mechanism in which the aldehyde component is aiding in the allylic transposition by forming a covalent adduct **4a** en route to intermediate **4b** (Scheme 5). In addition, mixtures of **4** and **4c** can be isolated after column chromatography for further analysis (see Supporting Information for details). However, as the desired Baylis–Hillman products **11** were obtained as principal products from this reaction, we surmise that **4b** co-exists in an inconsequential equilibrium with **4** from which only **4** is partaking in the overall transformation. To confirm the connectivity of products **11**, an X-ray crystal structure of derivative **11a** was obtained. In agreement with NMR-spectroscopy, the X-ray diffraction experiments confirmed that these products **11a–d** are formed as mixtures of diastereoisomers (d.r. ~1:1)[7] indicating that in this instance the more remote tertiary alcohol is not controlling the stereochemistry (Figure 3).

In summary, we have developed efficient routes for the functionalization of a versatile cyclopentenone building block that was previously accessed via a continuous flow sequence from D-glucono-1,5-lactone. Initially, we investigated the aza-Michael addition of different anilines resulting in the diastereoselective formation of the corresponding adducts. We furthermore demonstrated the functionalization of the α-position of the cyclopentenone substrate via a Baylis–Hillman reaction. Whereas the desired products
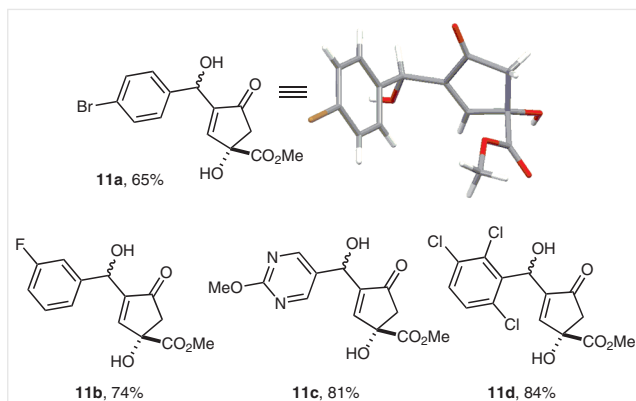
Figure 3 Baylis–Hillman products and X-ray crystal structure of **11a**

were obtained as mixtures of diastereoisomers, we discovered a complementary allylic transposition pathway that appears to be mediated by the aldehyde substrate, which we will investigate in due course.

Unless otherwise stated, all solvents were purchased from Fisher Scientific and used without further purification. Substrates and reagents were purchased from Alfa Aesar or Sigma Aldrich and used as received.

^{1}H NMR spectra were recorded on Bruker Avance-400, Varian VNMRS-600 or Varian VNMRS-700 instruments and are reported relative to residual solvent: CHCl$_3$ (δ 7.26). ^{13}C NMR spectra were recorded on the same instruments and are reported relative to CHCl$_3$ (δ 77.16). Data for ^{1}H NMR are reported as follows: chemical shift (δ/ppm), multiplicity (standard abbreviations), coupling constant (Hz), integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ/ppm) and multiplicity (C, CH, CH$_2$, or CH$_3$). Data for ^{19}F NMR were recorded on the above instrument at a frequency of 376 MHz using CFCl$_3$ as external standard. DEPT-135, COSY, HSQC, HMBC, and NOESY experiments were used in the structural assignment. IR spectra were recorded on a PerkinElmer RX1 spectrophotometer (neat, ATR sampling) with the intensities of the characteristic signals being reported as weak (w, <20% of tallest signal), medium (m, 21–70% of tallest signal), or strong (s, >71% of tallest signal). Low- and high-resolution mass spectrometry were performed using the indicated techniques on either Waters LCT Premier XE or Waters TQD instruments equipped with Acquity UPLC and a lock-mass electrospray ion source.

Aminohydroxycyclopentanones 9a–i; General Procedure

The respective aniline **8** (1 mmol, 1.0 equiv) was added to a solution of cyclopentenone **4** (1 mmol, 1.0 equiv, 3 M, MeCN). The resulting mixture was heated at 75 °C and monitored by ^{1}H NMR spectroscopy. Once complete conversion of substrates was observed (6–12 h), the reaction mixture was evaporated and purified by silica column chromatography using EtOAc/hexanes (10–30% EtOAc) as solvent system. After evaporation of the volatiles, the desired products were typically isolated as yellow oils that solidified upon standing.

Methyl *rac*-(1*S*,2*R*)-2-[(4-Chlorophenyl)amino]-1-hydroxy-4-oxo-cyclopentanecarboxylate (9a)

Yellow oil; yield: 221 mg (78%).

IR (neat): 3386 (m), 2955 (w), 1737 (s), 1599 (s), 1492 (s), 1398 (m), 1316 (m), 1277 (m), 1234 (s), 1179 (s), 1091 (s), 1029 (m), 818 (s), 753 (s), 501 cm^{-1} (m).

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.10 (d, *J* = 8.9 Hz, 2 H), 6.55 (d, *J* = 8.9 Hz, 2 H), 4.48 (dd, *J* = 10.9, 7.9 Hz, 1 H), 3.88 (br s, 1 H), 3.74 (s, 3 H), 2.79–2.89 (m, 2 H), 2.61 (d, *J* = 18.2 Hz, 1 H), 2.30 (ddd, *J* = 18.3, 10.9, 1.8 Hz, 1 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 210.6 (C), 174.0 (C), 144.9 (C), 129.2 (2 × CH), 123.4 (C), 115.1 (2 × CH), 78.7 (C), 57.4 (CH), 53.6 (CH$_3$), 50.7 (CH$_2$), 42.2 (CH$_2$).

HRMS (ASAP): *m/z* [M + H]$^+$ calcd for C$_{13}$H$_{15}$ClNO$_4$: 284.0690; found: 284.0688.

Methyl *rac*-(1*S*,2*R*)-2-[(3-Bromophenyl)amino]-1-hydroxy-4-oxo-cyclopentanecarboxylate (9b)

Yellow oil; yield: 275 mg (84%).

IR (neat): 3392 (m), 2955 (w), 1737 (s), 1595 (s), 1505 (m), 1481 (m), 1266 (m), 1235 (s), 1198 (s), 1164 (s), 1089 (s), 987 (s), 756 (s), 734 (s), 682 (m), 480 cm^{-1} (m).

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.01 (t, *J* = 8.0 Hz, 1 H), 6.86 (ddd, *J* = 7.8, 1.8, 0.9 Hz, 1 H), 6.77 (t, *J* = 2.1 Hz, 1 H), 6.54 (ddd, *J* = 8.2, 2.4, 0.9 Hz, 1 H), 4.51 (dd, *J* = 11.0, 7.9 Hz, 1 H), 4.26 (br s, 1 H), 3.80 (s, 3 H), 2.81–2.92 (m, 2 H), 2.62 (d, *J* = 18.2 Hz, 1 H), 2.32 (ddd, *J* = 18.2, 10.9, 1.8 Hz, 1 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 210.3 (C), 173.9 (C), 147.6 (C), 130.7 (CH), 123.4 (C), 121.6 (CH), 116.3 (CH), 112.9 (CH), 78.6 (C), 56.9 (CH), 53.8 (CH$_3$), 50.6 (CH$_2$), 42.3 (CH$_2$).

HRMS (ASAP): *m/z* [M + H]$^+$ calcd for C$_{13}$H$_{15}$BrNO$_4$: 328.0184; found: 328.0172.

Methyl *rac*-(1*S*,2*R*)-2-[(4-Bromophenyl)amino]-1-hydroxy-4-oxo-cyclopentanecarboxylate (9c)

Brown oil; yield: 265 mg (81%).

IR (neat): 3476 (m), 3383 (m), 2957 (w), 1737 (s), 1593 (s), 1489 (s), 1437 (m), 1397 (m), 1316 (m), 1278 (m), 1235 (s), 1179 (s), 1074 (m), 908 (s), 815 (s), 728 (s), 648 (m), 499 cm^{-1} (m).

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.26 (d, *J* = 8.0 Hz, 2 H), 6.53 (d, *J* = 8.0 Hz, 2 H), 4.51 (app q, *J* = 8.7 Hz, 1 H), 4.25 (d, *J* = 9.1 Hz, 1 H), 3.78 (s, 3 H), 2.83–2.92 (m, 2 H), 2.64 (d, *J* = 18.3 Hz, 1 H), 2.33 (ddd, *J* = 18.3, 10.8, 1.8 Hz, 1 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 210.4 (C), 174.0 (C), 145.3 (C), 132.1 (2 × CH), 115.6 (2 × CH), 110.5 (C), 78.7 (C), 57.2 (CH), 53.7 (CH$_3$), 50.7 (CH$_2$), 42.3 (CH$_2$).

HRMS (ASAP): *m/z* [M + H]$^+$ calcd for C$_{13}$H$_{15}$BrNO$_4$: 328.0184; found: 328.0193.

Methyl *rac*-(1*S*,2*R*)-2-(*m*-Tolylamino)-1-hydroxy-4-oxocyclopen-tanecarboxylate (9d)

Yellow oil; yield: 233 mg (89%).

IR (neat): 3391 (m), 2959 (w), 1739 (s), 1606 (m), 1490 (m), 1437 (m), 1235 (m), 1167 (s), 1096 (m), 1030 (m), 909 (s), 772 (s), 728 (s), 692 (s), 648 (m), 440 cm^{-1} (m).

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.07 (app t, *J* = 7.6 Hz, 1 H), 6.60 (d, *J* = 7.6 Hz, 1 H), 6.40–6.50 (m, 2 H), 4.54 (app q, *J* = 10.0 Hz, 1 H), 4.09 (d, *J* = 9.6 Hz, 1 H), 3.75 (s, 3 H), 2.80–2.92 (m, 2 H), 2.65 (d, *J* = 18.4 Hz, 1 H), 2.32 (ddd, *J* = 18.4, 11.0, 1.8 Hz, 1 H), 2.27 (s, 3 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 210.8 (C), 174.1 (C), 146.2 (C), 139.2 (C), 129.3 (CH), 119.8 (CH), 114.8 (CH), 111.1 (CH), 78.8 (C), 57.4 (CH), 53.5 (CH$_3$), 50.6 (CH$_2$), 42.5 (CH$_2$), 21.6 (CH$_3$).

HRMS (ES): m/z [M + H]$^+$ calcd for C$_{14}$H$_{18}$NO$_4$: 264.1236; found: 264.1237.

Methyl rac-(1S,2R)-2-[(3-Methoxyphenyl)amino]-1-hydroxy-4-oxocyclopentanecarboxylate (9e)

Orange oil; yield: 254 mg (91%).

IR (neat): 3437 (m), 3359 (m), 2963 (w), 1733 (s), 1595 (s), 1492 (m), 1230 (s), 1172 (s), 1126 (s), 1026 (s), 973 (m), 839 (s), 774 (m), 756 (m), 692 (m), 498 cm^{-1} (m).

^{1}H NMR (CDCl$_3$, 600 MHz): δ = 7.06 (app t, J = 8.2 Hz, 1 H), 6.30 (ddd, J = 8.2, 2.3, 0.8 Hz, 1 H), 6.23 (ddd, J = 8.2, 2.3, 0.8 Hz, 1 H), 6.18 (app t, J = 2.3 Hz, 1 H), 4.51 (app t, J = 9.4 Hz, 1 H), 4.17 (s, 1 H), 3.77 (s, 1 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 2.82–2.88 (m, 2 H), 2.61 (ddd, J = 18.2, 1.9, 0.8 Hz, 1 H), 2.30 (ddd, J = 18.2, 10.8, 1.9 Hz, 1 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ = 210.7 (C), 174.1 (C), 160.8 (C), 147.5 (C), 130.2 (CH), 106.8 (CH), 103.8 (CH), 100.2 (CH), 78.8 (C), 57.2 (CH), 55.1 (CH$_3$), 53.6 (CH$_3$), 50.6 (CH$_2$), 42.4 (CH$_2$).

HRMS (ES): m/z [M + H]$^+$ calcd for C$_{14}$H$_{18}$NO$_5$: 280.1185; found: 280.1163.

Methyl rac-(1S,2R)-2-{[4-Chloro-2,5-dimethoxyphenyl]amino}-1-hydroxy-4-oxocyclopentanecarboxylate (9f)

Brown oil; yield: 281 mg (82%).

IR (neat): 3395 (w), 2957 (w), 1747 (s), 1596 (m), 1515 (s), 1450 (s), 1398 (s), 1207 (s), 1159 (s), 1031 (s), 910 (m), 848 (m), 796 (m), 728 (s), 649 cm^{-1} (m).

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 6.76 (s, 1 H), 6.31 (s, 1 H), 4.51 (dd, J = 11.1, 7.9 Hz, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.70 (s, 3 H), 2.78–2.91 (m, 2 H), 2.65 (ddd, J = 18.2, 1.8, 0.9 Hz, 1 H), 2.32–2.43 (m, 1 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 210.4 (C), 174.0 (C), 149.6 (C), 141.7 (C), 135.5 (C), 112.4 (CH), 110.3 (C), 98.6 (CH), 78.7 (C), 57.8 (CH), 57.2 (CH$_3$), 56.2 (CH$_3$), 53.5 (CH$_3$), 50.6 (CH$_2$), 42.4 (CH$_2$).

HRMS (ES): m/z [M + H]$^+$ calcd for C$_{15}$H$_{19}$ClNO$_6$: 344.0901; found: 344.0900.

Methyl rac-(1S,2R)-2-[(5-Bromopyridin-3-yl)amino]-1-hydroxy-4-oxocyclopentanecarboxylate (9g)

Yellow oil; yield: 261 mg (79%).

IR (neat): 3358 (m), 2926 (m), 1739 (s), 1582 (s), 1518 (m), 1448 (m), 1234 (s), 1201 (s), 1161 (s), 1095 (s), 1031 (m), 1006 (m), 753 (s), 695 cm^{-1} (m).

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 8.02 (d, J = 1.9 Hz, 1 H), 7.92 (d, J = 2.6 Hz, 1 H), 7.07 (dd, J = 2.6, 1.9 Hz, 1 H), 4.46–4.56 (m, 2 H), 3.82 (s, 3 H), 2.81–2.92 (m, 2 H), 2.64 (ddd, J = 18.2, 19, 0.9 Hz, 1 H), 2.29–2.41 (m, 1 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 209.6 (C), 173.7 (C), 143.5 (C), 140.2 (CH), 134.9 (CH), 121.9 (CH), 121.1 (C), 78.6 (C), 56.4 (CH), 53.8 (CH$_3$), 50.7 (CH$_2$), 42.0 (CH$_2$).

HRMS (ASAP): m/z [M + H]$^+$ calcd for C$_{12}$H$_{14}$BrN$_2$O$_4$: 329.0137; found: 329.0122.

Methyl rac-(1S,2R)-2-{[3-(6-Methoxypyridin-3-yl)phenyl]amino}-1-hydroxy-4-oxocyclopentanecarboxylate (9h)

Yellow oil; yield: 238 mg (67%).

IR (neat): 3383 (w), 2952 (w), 1740 (s), 1604 (s), 1481 (s), 1366 (m), 1283 (s), 1235 (s), 1173 (s), 1021 (s), 832 (m), 752 (s), 697 (m), 609 cm^{-1} (m).

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 8.33 (dd, J = 2.6, 0.7 Hz, 1 H), 7.72 (dd, J = 8.6, 2.6 Hz, 1 H), 7.21 (app t, J = 7.8 Hz, 1 H), 6.85–6.90 (m, 1 H), 6.73–6.80 (m, 2 H), 6.60 (ddd, J = 8.2, 2.4, 0.9 Hz, 1 H), 4.60 (dd, J = 10.8, 7.8 Hz, 1 H), 4.41 (br s, 1 H), 4.16 (br s, 1 H), 3.67 (s, 3 H), 3.67 (s, 3 H), 2.82–2.94 (m, 2 H), 2.59–2.67 (m, 1 H), 2.35 (ddd, J = 18.8, 10.8, 1.8 Hz, 1 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 211.0 (C), 174.0 (C), 163.6 (C), 146.8 (C), 144.9 (CH), 139.1 (C), 137.5 (CH), 130.1 (C), 130.0 (CH), 117.2 (CH), 112.9 (CH), 112.2 (CH), 110.6 (CH), 78.9 (C), 57.3 (CH), 53.6 (CH$_3$), 53.5 (CH$_3$), 50.7 (CH$_2$), 42.3 (CH$_2$).

HRMS (ASAP): m/z [M + H]$^+$ calcd for C$_{19}$H$_{21}$N$_2$O$_5$: 357.1450; found: 357.1452.

Methyl rac-(1S,2R)-2-[(3-Fluoro-4-methylphenyl)amino]-1-hydroxy-4-oxocyclopentanecarboxylate (9i)

Yellow oil; 233 mg (83%).

IR (neat): 3384 (m), 2956 (w), 1736 (s), 1633 (s), 1589 (m), 1516 (s), 1438 (m), 1326 (m), 1266 (m), 1235 (s), 1159 (s), 1114 (s), 1029 (m), 838 (m), 803 (m), 735 (s), 626 (m), 454 cm^{-1} (m).

^{1}H NMR (CDCl$_3$, 600 MHz): δ = 6.90–6.96 (m, 1 H), 6.29–6.33 (m, 2 H), 4.46 (ddd, J = 11.0, 10.0, 7.9 Hz, 1 H), 4.11 (d, J = 8.8 Hz, 1 H), 3.77 (s, 3 H), 3.70 (s, 1 H), 2.82–2.88 (m, 2 H), 2.61 (ddd, J = 18.3, 1.9, 0.9 Hz, 1 H), 2.27–2.33 (m, 1 H), 2.13 (d, J = 1.3 Hz, 3 H).

^{13}C NMR (CDCl$_3$, 151 MHz): δ = 210.3 (C), 174.0 (C), 161.9 (d, J = 243 Hz, C), 145.7 (d, J = 11 Hz, C), 131.9 (d, J = 8 Hz, CH), 114.5 (d, J = 18 Hz, C), 109.7 (d, J = 2 Hz, CH), 100.9 (d, J = 26 Hz, CH), 78.6 (C), 57.4 (CH), 53.6 (CH$_3$), 50.6 (CH$_2$), 42.3 (CH$_2$), 13.6 (CH$_3$).

^{19}F NMR (CDCl$_3$, 376 MHz): δ = –116.3 (s).

HRMS (ASAP): m/z [M + H]$^+$ calcd for C$_{14}$H$_{17}$FNO$_4$: 282.1142; found: 282.1158.

Baylis–Hillman Adducts 11a–d; General Procedure

Cyclopentenone **4** (0.8 mmol, 1.0 equiv), DABCO (0.2 mmol, 0.25 equiv), and the aldehyde component **10** (1.0 mmol, 1.25 equiv) were dissolved in a mixture of THF and CHCl$_3$ (1:1 v/v, 1.5 M) and stirred at 40 °C for 10 h. After completion of the reaction was indicated by TLC (20% EtOAc/hexanes), the solvents were evaporated and the crude product was purified by silica column chromatography 10–30% EtOAc/hexanes) to yield a mixture of co-polar reaction products. It was found possible to crystalize the less soluble diastereomer of **11** using CHCl$_3$ or Et$_2$O as solvent.

Methyl 3-[(4-Bromophenyl)(hydroxy)methyl]-1-hydroxy-4-cyclopent-2-enecarboxylate (11a)

Brown oil; yield: 177 mg (65%).

IR (neat): 3418 (br), 2956 (w), 1714 (s), 1488 (m), 1437 (m), 1402 (m), 1258 (s), 1198 (s), 1171 (s), 1071 (s), 1011 (m), 832 cm^{-1} (m).

Diastereomer A

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.47 (d, J = 8.4 Hz, 2 H), 7.25 (d, J = 8.4 Hz, 2 H), 6.98 (s, 1 H), 3.81 (s, 3 H), 2.98 (br s, 1 H), 2.95 (d, J = 18.4 Hz, 1 H), 2.60 (d, J = 18.4 Hz, 1 H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ = 203.9 (C), 173.9 (C), 153.8 (CH), 149.2 (C), 139.1 (C), 131.8 (2 × CH), 128.3 (2 × CH), 122.3 (C), 76.9 (C), 68.9 (CH), 54.0 (CH$_2$), 48.3 (CH$_2$).

Diastereomer B

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.47 (d, J = 8.4 Hz, 2 H), 7.24 (d, J = 8.4 Hz, 2 H), 6.98 (s, 1 H), 5.52 (s, 1 H), 3.79 (s, 3 H), 3.03 (br s, 1 H), 2.92 (d, J = 18.4 Hz, 1 H), 2.65 (d, J = 18.4 Hz, 1 H).

^{13}C NMR (CDCl$_3$, 176 MHz): δ = 204.1 (C), 173.8 (C), 154.2 (CH), 149.1 (C), 138.3 (C), 131.8 (2 × CH), 128.3 (2 × CH), 122.3 (C), 77.0 (C), 68.9 (CH), 53.9 (CH$_3$), 48.2 (CH$_2$).

HRMS (ASAP): m/z [M – OH]$^+$ calcd for C$_{14}$H$_{12}$BrO$_4$: 322.9919; found: 322.9932.

Methyl 3-[(3-Fluorophenyl)(hydroxy)methyl]-1-hydroxy-4-cyclopent-2-enecarboxylate (11b)

Yellow oil; yield: 166 mg (74%).

IR (neat): 3424 (br), 2957 (w), 1711 (s), 1591 (m), 1487 (m), 1438 (m), 1244 (s), 1198 (m), 1170 (m), 1082 (m), 911 (m), 789 (m), 758 (m), 731 (m), 702 cm^{-1} (m).

Diastereomer A

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.29–7.35 (m, 1 H), 7.13–7.18 (m, 1 H), 7.07 (dt, J = 9.7, 2.0 Hz, 1 H), 6.97–7.03 (m, 2 H), 5.96 (s, 1 H), 3.80 (s, 3 H), 2.93 (d, J = 18.4 Hz, 1 H), 2.65 (d, J = 18.4 Hz, 1 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 204.0 (C), 173.9 (C), 162.9 (CF, d, J = 244 Hz), 154.4 (CH), 149.2 (C), 142.7 (C, d, J = 7 Hz), 130.3 (CH, d, J = 8 Hz), 122.4 (CH, d, J = 3 Hz), 115.2 (CH, d, J = 21 Hz), 113.6 (CH, d, J = 22 Hz), 77.1 (C), 68.8 (CH, m), 54.0 (CH$_3$), 48.2 (CH$_2$).

^{19}F NMR (CDCl$_3$, 376 MHz): δ = –112.4 (s).

Diastereomer B

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.29–7.35 (m, 1 H), 7.13–7.18 (m, 1 H), 7.11 (dt, J = 9.7, 2.0 Hz, 1 H), 6.97–7.03 (m, 2 H), 5.98 (s, 1 H), 3.82 (s, 3 H), 2.96 (d, J = 18.4 Hz, 1 H), 2.62 (d, J = 18.4 Hz, 1 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 204.0 (C), 173.9 (C), 162.9 (CF, d, J = 244 Hz), 154.1 (CH), 149.1 (C), 142.7 (d, J = 7 Hz), 130.3 (CH, d, J = 8 Hz), 122.2 (CH, d, J = 3 Hz), 115.2 (CH, d, J = 21 Hz), 113.5 (CH, d, J = 22 Hz), 77.2 (C), 68.8 (CH, m), 54.0 (CH$_3$), 48.3 (CH$_2$).

^{19}F NMR (CDCl$_3$, 376 MHz): δ = –112.2 (s).

HRMS (ES): m/z [M – OH]$^+$ calcd for C$_{14}$H$_{12}$FO$_4$: 263.0714; found: 263.0737.

Methyl 1-Hydroxy-3-[hydroxy(2-methoxypyrimidin-5-yl)methyl]-4-oxocyclopent-2-enecarboxylate (11c)

Yellow oil; yield: 191 mg (81%).

IR (neat): 3457 (m), 3171 (br), 1741 (s), 1713 (s), 1600 (m), 1570 (m), 1478 (s), 1407 (s), 1331 (m), 1272 (s), 1197 (m), 1168 (m), 1031 (s), 804 cm^{-1} (m).

Diastereomer A

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 8.53 (s, 2 H), 7.12 (d, J = 1.4 Hz, 1 H), 5.60 (d, J = 1.4 Hz, 1 H), 4.01 (s, 3 H), 3.84 (s, 3 H), 2.99 (d, J = 18.4 Hz, 1 H), 2.64 (d, J = 18.4 Hz, 1 H), 2.17 (br s, 1 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 203.8 (C), 173.7 (C), 165.5 (C), 158.1 (2 × CH), 154.2 (CH), 148.3 (C), 127.1 (C), 77.2 (C), 65.6 (CH), 55.2 (CH$_3$), 54.1 (CH$_3$), 48.3 (CH$_2$).

Diastereomer B

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 8.48 (s, 2 H), 7.24 (s, 1 H), 5.56 (s, 1 H), 3.99 (s, 3 H), 3.79 (s, 3 H), 3.20 (br s, 2 H), 2.93 (d, J = 18.4 Hz, 1 H), 2.66 (d, J = 18.4 Hz, 1 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 203.6 (C), 173.6 (C), 165.3 (C), 158.2 (2CH), 154.6 (CH), 148.7 (C), 127.3 (C), 77.2 (C), 65.1 (CH), 55.2 (CH$_3$), 54.0 (CH$_3$), 48.3 (CH$_2$).

HRMS (ES): m/z [M + H]$^+$ calcd for C$_{13}$H$_{15}$N$_2$O$_6$: 295.0930; found: 295.0932.

Methyl 1-Hydroxy-3-[hydroxy(2,3,6-trichlorophenyl)methyl]-4-oxocyclopent-2-enecarboxylate (11d)

Yellow oil; yield: 244 mg (84%).

IR (neat): 3421 (br), 2956 (w), 1712 (s), 1436 (s), 1322 (m), 1249 (s), 1192 (s), 1172 (s), 1092 (s), 1025 (m), 1010 (m), 913 (m), 912 (s), 771 (m), 731 cm^{-1} (s).

Diastereomer A

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.39 (d, J = 8.7 Hz, 1 H), 7.28 (d, J = 8.7 Hz, 1 H), 7.14 (d, J = 2.1 Hz, 1 H), 6.39 (d, J = 5.2 Hz, 1 H), 3.81 (s, 3 H), 3.79 (s, 1 H), 3.61 (d, J = 7.0 Hz, 1 H), 2.95 (d, J = 18.3 Hz, 1 H), 2.68 (d, J = 18.3 Hz, 1 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 202.9 (C), 174.0 (C), 154.8 (CH), 146.8 (C), 136.6 (C), 133.7 (C), 133.5 (C), 132.9 (C), 130.6 (CH), 129.5 (CH), 76.8 (C), 68.1 (CH), 53.9 (CH$_3$), 48.2 (CH$_2$).

Diastereomer B

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.32 (d, J = 8.7 Hz, 1 H), 7.21 (d, J = 8.7 Hz, 1 H), 7.20 (d, J = 2.1 Hz, 1 H), 6.29 (d, J = 2.0 Hz, 1 H), 4.11 (br s, 2 H), 3.74 (s, 3 H), 2.90 (d, J = 18.4 Hz, 1 H), 2.59 (d, J = 18.4 Hz, 1 H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ = 203.0 (C), 173.8 (C), 155.4 (CH), 147.0 (C), 136.4 (C), 133.7 (C), 132.8 (C), 130.5 (CH), 129.4 (CH), 77.0 (C), 67.7 (CH), 53.7 (CH$_3$), 48.2 (CH$_2$).

HRMS (ASAP): m/z [M – OH]$^+$ calcd for C$_{14}$H$_{10}$Cl$_3$O$_4$: 346.9645; found: 346.9650.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591745.

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(6) CCDC 1581502 (**9e**), and CCDC 1581503 (**9g**), and CCDC 1581504 (**11**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(7) Although separation of these diastereoisomers was found challenging by silica gel chromatography, fractional crystallization from solutions of structures **11** in Et$_2$O was found possible.[6]