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π-Allyl palladium approach toward the diazabicyclo[3.2.1]octane core of the naphthyridinomycin alkaloids

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Abstract—A novel and efficient protocol for the synthesis of the 3,8-diazabicyclo[3.2.1]octane system found in the naphthyridinomycin, dnacin, and tetrazomine families of alkaloids is described. The key transformation involves an intramolecular palladium-catalyzed allylic alkylation. The cyclization proceeds smoothly under mild conditions (20 mol % Pd_2dba_3, 1.5 equiv DBU, 65 °C, THF, 20 min) to afford 3,8-diazabicyclo[3.2.1]octanes in excellent yields (94–98%).

1. Introduction

Over the past three decades, antitumor antibiotics belonging to the tetrahydroisoquinoline alkaloid family have been extensively investigated.[1] These natural products which include saframycin, naphthyridinomycin/bioxalomycin, and quinocarcin/tetrazomine exhibit a wide range of biological activities, such as antitumor, antifungal, antimicrobial activities, and others.[1–5] Dnacins A_1 (**1**) and B_1 (**2**) are new members of the naphthyridinomycin/bioxalomycin class, isolated from *Actinosynnema pretiosum* C-14482 in 1980,[2] although their structures were not determined until 1994.[3] Interestingly, dnacin B_1 (**2**) is structurally equivalent to naphthyridinomycin (**3**) with the exception of the amino group at C_{11} and the hydrogen atom at C_{12}.[3] Akin to naphthyridinomycin, dnacin B_1 inhibits DNA synthesis as evidenced by its ability to prevent the incorporation of ^{3}H-thymidine into DNA, and it has been shown to cleave DNA by the formation of superoxide.[4] Both dnacins A_1 and B_1 have been recognized as novel inhibitors of Cdc25 phosphatase,[5] thereby broadening their potential for use as chemotherapeutics. Inspired by the wide range of biological activities and the structural complexity of these alkaloids, several total syntheses and a number of partial synthesis efforts have been documented.[6] Nonetheless, more practical and efficient routes to these natural products that would allow an improved stereocontrol in the assembly of the core structure need to be developed.

As a general strategy toward the synthesis of naphthyridinomycins, we envisioned two distinct approaches for the construction of the 3,8-diazabicyclo[3.2.1]octane core structures **5** and **6**, which are embedded in all targets shown in Figure 1: the palladium-catalyzed intramolecular Heck cyclization of vinyl phosphate **7** (Fig. 2, route A) and the palladium-catalyzed intramolecular allylic alkylation of malonate **8** (Fig. 2, route B). By employing the intramolecular processes, the configuration at the stereogenic C_1 (*) in bicycles **5** and **6** should derive from the attachment of the

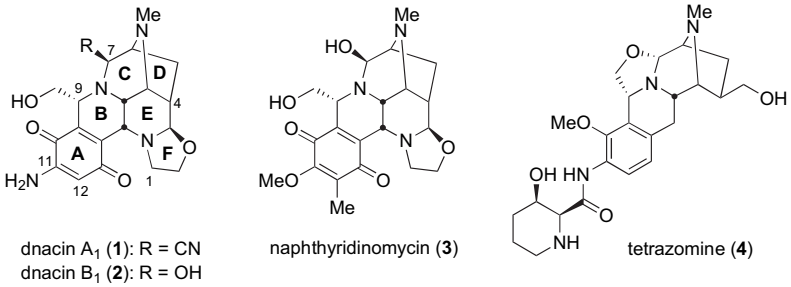

Figure 1. Selected examples of natural products containing the 3,8-diazabicyclo[3.2.1]octane core (C,D-ring system).

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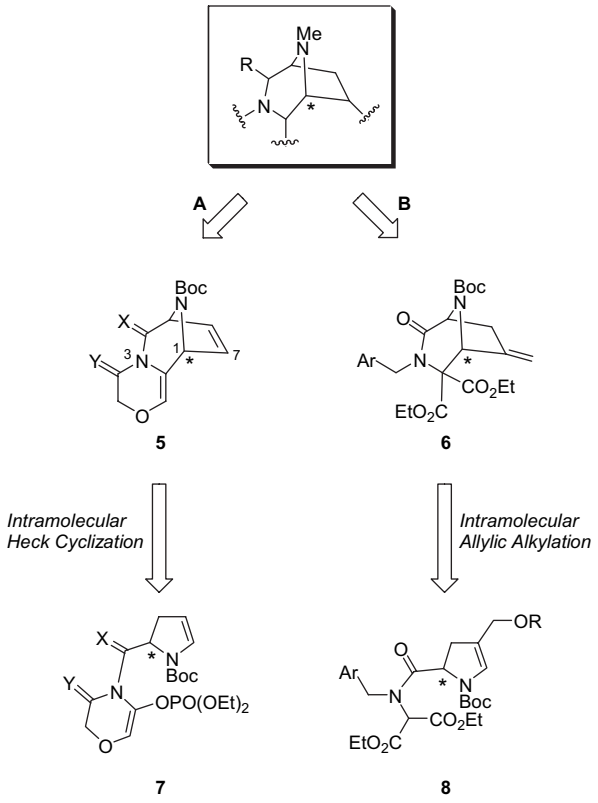
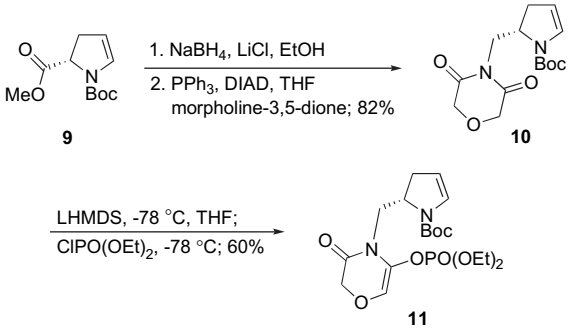


Figure 2. Retrosynthetic analysis of dnacins and related compounds.

tether in precursors **7** and **8**. Furthermore, both **5** and **6** provide adequate functionalization for the introduction of the remaining substituents in dnacins and related naphthyridinomycins. In this report, we describe our pursuit of these new synthetic routes toward the 3,8-diazabicyclo[3.2.1]-octane ring system.

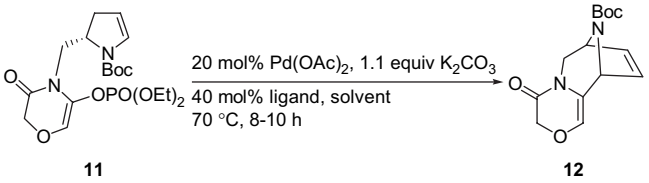
2. Results and discussion

Our initial strategy for the synthesis of 3,8-diazabicyclo[3.2.1]octanes relied upon the intramolecular Heck cyclization (Fig. 2, route A). Although a large number of Heck reactions have been applied to natural product syntheses,[7] only a handful of examples have been documented for the construction of bridged bicyclic ring systems.[8] As outlined in Scheme 1, starting from the known ester **9** derived from (*S*)-pyroglutamic acid,[9] vinyl phosphate **11** was prepared in three steps. The vinyl phosphate was chosen to explore the key Heck cyclization because vinyl phosphates[10a–e] were found to be more reactive than the corresponding triflates.[10f] Hence, reduction of **9** with $NaBH_4$/LiCl, followed by Mitsunobu reaction with morpholine-3,5-dione, afforded **10** in 82% yield (two steps). The desired Heck precursor **11** was subsequently obtained in 60% yield by treatment of **10** with LHMDS (−78 °C, THF) followed by slow addition of diethyl chlorophosphate (Scheme 1). With the desired precursor in hand, the key intramolecular Heck cyclization was explored under several different reaction conditions (Table 1). With $Pd(OAc)_2$ and dppf as a ligand (70 °C, THF), cyclization failed completely (entry 1). After several attempts, we found that bidentate ligands and K_2CO_3 as a base were most effective. Several bidentate ligands and reaction parameters were screened, and dppp as a ligand in DME or THF (Table 1, entries 5–7) provided the desired product **12** in modest yields (45–53%). A similar result was obtained when the cyclization of **11** was carried out under microwave heating at 100 °C for 30 min (54%, entry 8).[11]



Scheme 1.

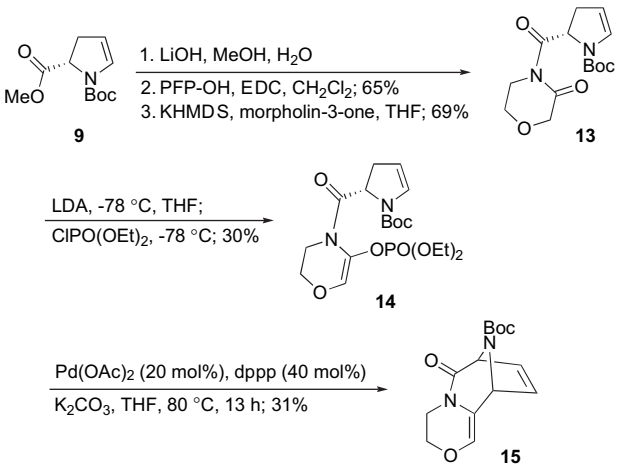
Table 1. Optimization of Heck cyclization of vinyl phosphate **11**



Entry	Ligand	Solvent	Product **12** (%)	Starting material **11** (%)
1	dppf	THF	—	—
2	BINAP	THF	12	—
3	dppe	THF	13	25
4	dppb	DME	36	22
5	dppp	THF	41	7
6	dppp	DME	45	21
7[a]	dppp	DME	53	<5
8[a,b]	dppp	DME	54	—

[a] $Pd(OAc)_2$ (40 mol %) and dppp (80 mol %) were used.
[b] Reaction mixture was heated in the microwave at 100 °C for 30 min.

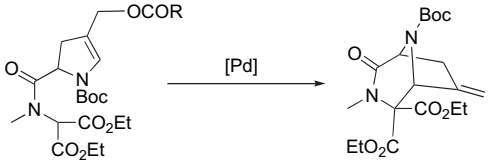
To further explore the scope of the Heck cyclization for the construction of the 3,8-diazabicyclo[3.2.1]octane unit, we extended this chemistry to a vinyl phosphate substrate bearing a carbonyl group adjacent to a bridgehead carbon (Scheme 2). Hydrolysis of **9** followed by EDC-promoted esterification with pentafluorophenol (PFP-OH) afforded the activated ester, which was transformed into amide **13** upon treatment with morpholin-3-one and KHMDS (45%, three steps). The Heck precursor **14** was then obtained by treating **13** with LDA (−78 °C, THF) followed by trapping of the enolate anion with diethyl chlorophosphate. Whereas the Heck cyclization of **11** led to the desired 3,8-diazabicyclo[3.2.1]octane **12** in modest yields, cyclization of derivative **14** was sluggish and provided the cyclized product **15** in low yield (31%) under optimized conditions (20 mol % $Pd(OAc)_2$, 40 mol % dppp, 1.1 equiv K_2CO_3 in DME, Scheme 2). Presumably, the poor reactivity of **14** can be attributed to the increased ring strain during the cyclization due to incorporation of an sp^2-hybridized carbon in the tether. In all cases, the Heck cyclization required high catalyst loadings (up to 40 mol % of Pd) and long reaction times for complete conversion.



Scheme 2.

Due to these limitations in route A, an alternative strategy was considered in order to improve the synthesis of the 3,8-diazabicyclo[3.2.1]octane system, and we turned our attention to the intramolecular allylic alkylation methodology (Fig. 2, route B). Although inter- and intramolecular allylic alkylations have been used extensively in complex natural product synthesis,[7h,12] the application of this chemistry to the preparation of bridged carbo- and heterocyclic ring systems is less frequent.[13] For our initial investigations, the key precursors **22a–c** were synthesized from the known aldehyde **16** in eight steps (Scheme 3).[14] Aldehyde **16** underwent *N*-Boc protection, $NaBH_4$ reduction, *O*-TBS protection, and ester hydrolysis to afford acid **19** in 39% overall yield. Subsequently, acid **19** was coupled with sarcosine ethyl ester to afford amide **20** using DCC and HOBt (54%). Treatment of **20** with LHMDS, followed by addition of ethyl chloroformate (−78 °C, THF) furnished the malonate **21** in excellent yield (95%). Several allylic substrates were prepared to examine the palladium-catalyzed allylic alkylation. Desilylation of **21** with TBAF followed by O-acylations provided the allylic substrates **22a–c**. Initially, the allylic carbonate **22a** was examined due to the high reactivity of these derivatives toward allylic alkylation.[15] However, the carbonate was found to be very unstable and decomposed during reaction workup. Therefore, a more stable allylic benzoate **22b** was prepared and subjected to allylic alkylation conditions. Treatment of **22b** with $Pd(OAc)_2$ and dppe in the presence of base such as NaH or DBU in THF gave the cycloadduct **23** in 67 and 71% yields, respectively (Table 2, entries 1 and 2). Encouraged by these results, we then screened different allylic substrates and catalysts. Under the same conditions, the pivaloate **22c** afforded **23** in higher yields (entries 3

Table 2. Optimization of allylic alkylations of malonates **22b** and **22c**

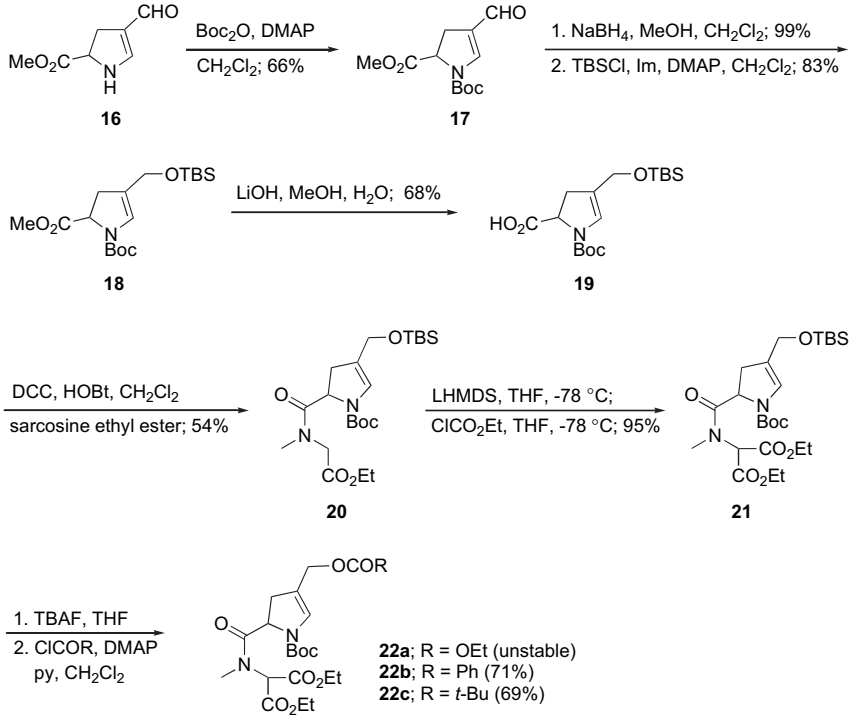


22b; R = Ph
22c; R = *t*-Bu

23

Entry	R	Catalyst	Base	Time (h)	Yield (%)[a]
1	Ph	$Pd(OAc)_2$/dppe	NaH	1	67
2	Ph	$Pd(OAc)_2$/dppe	DBU	4	71
3	*t*-Bu	$Pd(OAc)_2$/dppe	NaH	1	80
4	*t*-Bu	$Pd(OAc)_2$/dppe	DBU	4	83
5	*t*-Bu	$Pd(PPh_3)_4$	DBU	4	95
6	*t*-Bu	Pd_2dba_3	DBU	2	98

[a] Standard conditions: 10% palladium catalyst, 20% ligand, 1.5 equiv base, THF (0.02–0.05 M) at 65 °C.

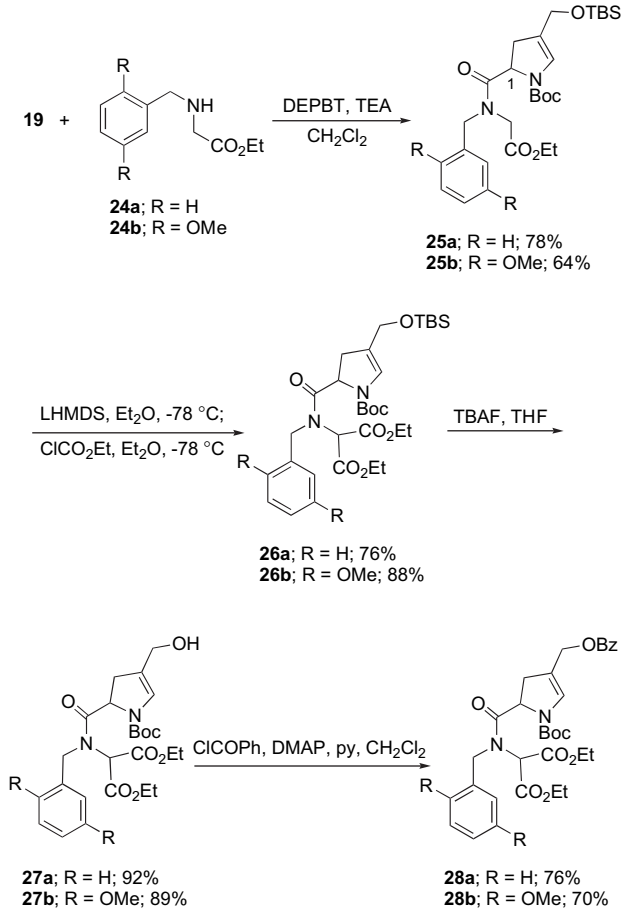


22a; R = OEt (unstable)
22b; R = Ph (71%)
22c; R = *t*-Bu (69%)

Scheme 3.

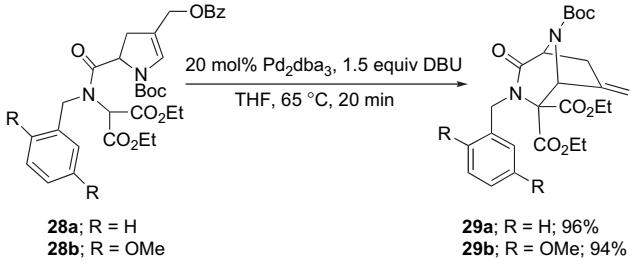
and 4). Furthermore, cycloadducts were formed in excellent yields by employing $Pd(PPh_3)_4$ and Pd_2dba_3 (entries 5 and 6).

To test the efficacy of this new methodology for the preparation of the 3,8-diazabicyclo[3.2.1]octane core structure in our natural product targets, we introduced the aromatic dnacin A-ring into the malonate moiety (Scheme 4). DEPBT-promoted[16] coupling of **19** and *N*-benzylglycine ethyl ester (**24a**) gave amide **25a** in good yield (78%). In a similar manner, amide **25b** was prepared from the coupling of **19** and *N*-(2,5-dimethoxy)benzylglycine ethyl ester **24b**, which is readily available from 2,5-dimethoxybenzylamine and ethyl bromoacetate.[17] At this stage, the A- and D-rings of the target molecule are present in the cyclization precursor (Scheme 4). Treatment of **25a** and **25b** with LHMDS followed by ethyl chloroformate provided malonates **26a** and **26b** (76 and 88%, respectively). It is noteworthy that excess amounts of LHMDS and ethyl chloroformate (6 equiv each) were necessary in order to drive the reaction to completion. An undesired acylation at C_1 of the pyrrolidine was not observed in either case, presumably due to steric hindrance around this position. Desilylations of **26a** and **26b** provided alcohols **27a** and **27b** in excellent yields of 92 and 89%, respectively.



Scheme 4.

The allylic pivaloate derivative of **27** was first chosen as a substrate due to its high reactivity toward Pd-catalyzed allylic alkylation. However, this pivaloate proved to be too unstable and decomposed during isolation. Alternatively, the allylic benzoates **28a** and **28b** were prepared using standard conditions (ClCOPh, DMAP, pyridine). The benzoates were significantly more stable than the pivaloates and could be purified by silica gel chromatography immediately after workup. However, extended storage must be avoided for intermediates **25**–**28** due to concomitant decomposition. With the key precursors in hand, the palladium-catalyzed allylic alkylations of **28a** and **28b** were studied (Scheme 5). To our delight, intramolecular allylic alkylations of **28a** and **28b** proceeded smoothly in the presence of 20 mol % of Pd_2dba_3 and 1.5 equiv of DBU in THF at 65 °C for 20 min to afford adducts **29a** and **29b** in excellent yields (96 and 94%, respectively).



Scheme 5.

3. Conclusion

We have developed two alternative approaches for the construction of the 3,8-diazabicyclo[3.2.1]octane ring system. Whereas the initial intramolecular Heck cyclization approach suffered from poor yields, the palladium-catalyzed intramolecular allylic alkylation provided an expedient route to these bridged heterocycles. To the best of our knowledge, this is the first time that a Pd-based route was used for the synthesis of the diazabicyclo[3.2.1]octane ring system. In addition, the functionalization of the 3,8-diazabicyclo-[3.2.1]octane core obtained from the intramolecular allylic alkylation protocol provides access to properly functionalized A,C,D-rings for the synthesis of dnacins and related naphthyridinomycin alkaloids. Since the Pd-coupling strategy is highly convergent and the two precursor segments are readily available in enantiomerically pure form, this strategy should lend itself to an asymmetric synthesis of the target molecules. Further improvements of this methodology and its application to natural product synthesis are currently in progress and will be reported in due course.

4. Experimental

4.1. General

All moisture-sensitive reactions were performed under an atmosphere of argon and glassware was flame dried under vacuum or dried in an oven at 150 °C prior to use. DME, THF, and Et_2O were dried by distillation over Na/Benzophenone; Et_3N and CH_2Cl_2 were dried by distillation over CaH_2, and KHMDS and LDA were prepared prior to use. Unless stated otherwise, solvents or reagents were used without further purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} plates (particle size 0.040–0.055 mm, 230–400 mesh) and

visualization was accomplished with a 254 nm UV light and/or by staining with $KMnO_4$ reagent (1.5 g of $KMnO_4$, 10 g of K_2CO_3, and 1.25 mL of 10% NaOH in 200 mL water). NMR spectra were recorded in $CDCl_3$ (298 K) at either 300.1 MHz (^1H) or 75.5 MHz (^{13}C) using a Bruker Avance 300 with XWIN-NMR software. Chemical shifts (δ) are reported in parts per million (ppm) with the residual solvent peak used as an internal standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br s=broad singlet, br d=broad doublet, br t=broad triplet, app.=apparent), coupling constants, and integration. Melting points were obtained using a heating rate of 2 °C min^{-1} on a MelTemp melting point apparatus with digital temperature reading and were reported uncorrected. Microwave heating was performed in an Emrys Optimizer single mode microwave reactor (Biotage) using 5 mL Emrys process vials.

4.1.1. 2-(3,5-Dioxomorpholin-4-ylmethyl)-2,3-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (10). To a mixture of $NaBH_4$ (499 mg, 13.2 mmol) and LiCl (560 mg, 13.2 mmol) in EtOH (18 mL) was added a solution of 2,3-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (**9**)[9] (1 g, 4.4 mmol) in THF (18 mL) at 0 °C. The reaction mixture was stirred at rt for 10 h, quenched with water (30 mL), and extracted with Et_2O (100 mL×2). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated to afford crude alcohol (861 mg).

To a solution of this alcohol (804 mg, 4.04 mmol), morpholine-3,5-dione (464 mg, 4.04 mmol), and PPh_3 (1.06 g, 4.04 mmol) in THF (20 mL) was added diazadiisopropyl dicarbonate (801 μL, 4.04 mmol) over 30 min (syringe pump) at rt. After 1 h, the solvent was removed in vacuo and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 8:2 to 6:4) to afford **10** (980 mg, 82%) as a pale yellow oily (6.3:1) mixture of rotamers: IR (neat) 2977, 1742, 1692, 1390, 1366 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.38 (br s, 1H), 4.96 (br s, 1H), 4.66 (br t, J=10.0 Hz, 1H), 4.41–4.19 (m, 6H), 3.49 (dd, J=12.1, 2.1 Hz, 1H), 2.87 (dd, J=16.4, 10.1 Hz, 1H), 2.14 (br d, J=16.4 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.7 (two peaks), 152.4, 129.4, 106.4, 80.2, 67.7 (two peaks), 53.8, 42.1, 33.6, 28.3; EIMS *m/z* (intensity) 297 ($[M+H]^+$, 5), 296 (M^+, 40), 223 (27), 68 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{20}N_2O_5$ 296.1372, found 296.1369.

4.1.2. 2-[5-(Diethoxyphosphoryloxy)-3-oxo-2,3-dihydro[1,4]oxazin-4-ylmethyl]-2,3-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (11). To a solution of **10** (300 mg, 1.01 mmol) in THF (11 mL) was added LHMDS (1.22 mL, 1.22 mmol) at −78 °C. After 20 min, the reaction mixture was allowed to warm to −30 °C and stirred at this temperature for 30 min. The mixture was cooled to −78 °C and a solution of diethyl chlorophosphate (176 μL, 1.22 mmol) in THF (3 mL) was added. After warming to 0 °C, the reaction mixture was quenched with 5% aqueous NH_4OH (4 mL), extracted with Et_2O (15 mL×3), washed with brine (5 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3, 1% NEt_3) to afford **11** (260 mg, 60%) as a pale yellow oily mixture of rotamers: IR (neat) 2980, 1704, 1619, 1402, 1360, 1278, 1226, 1183, 1134 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.55, 6.40 (2br s, 1H), 6.50 (d, J=2.9 Hz, 1H), 5.01, 4.93 (2br s, 1H), 4.54 (br s, 1H), 4.42–4.17 (m, 6H), 3.89, 3.85 (2d, J=7.2 Hz, 1H), 3.85–3.65 (m, 1H), 2.78 (dd, J=16.3, 10.1 Hz, 1H), 2.26 (br d, J=15.8 Hz, 1H), 1.47 (s, 9H), 1.38 (tt, J=7.1, 1.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 164.5, 134.1, 134.0, 129.5, 120.1 (2C), 106.1, 80.2, 68.0, 67.7, 65.4 (2C), 65.3, 64.4, 54.9, 42.2, 32.7, 28.3, 16.1, 16.0; EIMS *m/z* (intensity) 432 (M^+, 6), 265 (31), 178 (91), 68 (100); HRMS (EI) *m/z* calcd for $C_{18}H_{29}N_2O_8P$ 432.1662, found 432.1647.

4.1.3. 6-Oxo-4-oxa-7,12-diazatricyclo[7.2.1.$0^{2,7}$]dodeca-2,10-diene-12-carboxylic acid *tert*-butyl ester (12). *Table 1, entry 7*: $Pd(OAc)_2$ (4.4 mg, 0.02 mmol), dppp (16 mg, 0.04 mmol), and K_2CO_3 (15 mg, 0.11 mmol) were added to a solution of **11** (21 mg, 0.05 mmol) in DME (490 μL). This mixture was deoxygenated using freeze thaw cycles under vacuum and the reaction mixture was heated to 70 °C for 8 h. After cooling to rt, the mixture was diluted with brine (5 mL) and extracted with EtOAc (20 mL×2). The combined organic extracts were dried ($MgSO_4$), concentrated, and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3 to 1:1) to afford **12** (7.3 mg, 53%) as a colorless oily (2.4:1) mixture of rotamers: IR (neat) 2977, 1693, 1673, 1390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.21–6.15 (m, 2H), 6.12 (s, 1H), 4.84–4.64 (m, 2H), 4.39 (d, J=14.5 Hz, 1H), 4.22 (d, J=14.5 Hz, 1H), 3.65 (d, J=12.8 Hz, 1H), 3.43 (br s, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 164.1, 152.3, 133.8, 131.9, 125.8, 116.7, 80.7, 67.6, 56.1, 55.2, 40.7, 40.1, 28.2; EIMS *m/z* (intensity) 278 (M^+, 20), 222 (34), 57 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{18}N_2O_4$ 278.1267, found 278.1265.

Table 1, entry 8: $Pd(OAc)_2$ (5.2 mg, 0.023 mmol), dppp (19 mg, 0.046 mmol), and K_2CO_3 (16 mg, 0.108 mmol) were added to a solution of **11** (21 mg, 0.049 mmol) in DME (390 μL). The reaction mixture was stirred for 5 min and heated in the microwave for 30 min (hold time) at 100 °C. After cooling to rt, the mixture was diluted with brine (5 mL) and extracted with EtOAc (20 mL×2). The combined organic extracts were dried ($MgSO_4$), concentrated, and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3 to 1:1) to afford **12** (8.8 mg, 54%) as a colorless oil.

4.1.4. *tert*-Butyl 2-(3-oxomorpholine-4-carbonyl)-2,3-dihydropyrrole-1-carboxylate (13). To a solution of 2,3-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (**9**)[9] (6.5 g, 28.6 mmol) in MeOH (153 mL) was added LiOH (2.4 g, 57.2 mmol) followed by H_2O (39 mL) at 0 °C and the mixture was stirred at rt for 3 h. The reaction mixture was concentrated, and partitioned between water (80 mL) and Et_2O (50 mL×2). The aqueous layer was acidified to pH 2–4 with 3 N HCl and extracted with Et_2O (100 mL×3 and 50 mL×2). The combined extracts were dried ($MgSO_4$) and concentrated to give the crude acid. To a solution of the crude acid in CH_2Cl_2 (143 mL) was added pentafluorophenol (5.26 g, 28.6 mmol) followed by EDC (5.48 g, 28.6 mmol) at rt. Reaction mixture was stirred for 4.5 h, quenched with H_2O (100 mL), and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and the residue was purified

by chromatography on SiO_2 (hexanes/EtOAc, 9:1) to afford the activated ester (10.89 g, 65%) as a colorless oily (6.3:1) mixture of rotamers: IR (neat) 3120, 2982, 2936, 1800, 1716, 1522, 1458, 1398 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.79, 6.67 (2s, 1H), 5.20–5.00 (m, 2H), 3.46–3.26 (m, 1H), 3.10–2.92 (m, 1H), 1.58, 1.56 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ 167.8, 167.5, 151.2, 151.0, 142.9 (2C), 142.8, 142.7, 141.4, 139.5 (2C), 139.4, 137.9, 136.2, 130.1, 104.7, 81.8, 81.6, 57.8, 57.6, 35.8, 34.4, 28.2, 28.0; EIMS *m/z* (intensity) 379 (M^+, 20), 324 (60), 279 (75), 278 (65), 112 (62), 57 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{14}F_5NO_4$ 379.0843, found 379.0845.

A solution of morpholine-3-one (288 mg, 2.84 mmol) in THF (15 mL) was treated with KHMDS (5.7 mL, 2.84 mmol, 0.5 M in THF) dropwise at −78 °C and stirred for 1 h at this temperature. A solution of activated ester (863 mg, 2.28 mmol) in THF (10 mL) was then added and stirred for additional 0.5 h. Reaction mixture was quenched with a saturated aqueous NH_4Cl solution (10 mL), diluted with CH_2Cl_2 (10 mL) at −78 °C, and warmed to rt. Reaction mixture was extracted with CH_2Cl_2 (100 mL×2). The combined extracts were dried ($MgSO_3$), filtered, concentrated, and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3) to afford **13** (464 mg, 69%) as a colorless foamy (1.7:1) mixture of rotamers: IR (neat) 2976, 2869, 1704, 1623, 1461, 1401, 1310, 1285, 1250, 1203, 1136 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.71, 6.57 (2 m, 1H), 5.63–5.50 (m, 1H), 4.93–4.87 (m, 1H), 4.38–4.22 (m, 2H), 4.02–3.73 (m, 4H), 3.33–3.20 (m, 1H), 2.62–2.48 (m, 1H), 1.49, 1.41 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.6, 173.2, 169.2, 169.1, 151.3, 151.2, 130.3, 104.7, 104.6, 80.8, 80.4, 68.7 (2C), 63.9, 63.8, 61.4, 61.2, 43.7, 43.6, 35.8, 34.8, 28.3, 28.2; EIMS *m/z* (intensity) 297 ($[M+H]^+$, 7), 296 (M^+, 27), 222 (34), 57 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{20}N_2O_5$ 296.1372, found 296.1368.

4.1.5. *tert*-Butyl 2-(5-(diethoxyphosphoryloxy)-3,4-dihydro-2*H*-1,4-oxazine-4-carbonyl)-2,3-dihydropyrrole-1-carboxylate (14). A solution of **13** (213 mg, 0.78 mmol) in THF (8 mL) was treated with freshly prepared LDA (1.6 mL, 1.01 mmol, 0.65 M in THF) at −78 °C. The resulting mixture was slowly warmed up to −40 °C over 1 h, quenched with 5% aqueous NH_4OH solution (5 mL), and extracted with Et_2O (20 mL×3). The combined organic layers were washed with brine, dried ($MgSO_3$), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3 to 1:1, 1% NEt_3) to afford **14** (100 mg, 30%) as a colorless foamy (1.4:1) mixture of rotamers: IR (neat) 2978, 2933, 1702, 1392, 1327, 1275, 1196, 1167, 1116, 1029 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.71–6.70, 6.55–6.53 (2m, 1H), 6.47 (dd, *J*=8.8, 3.5 Hz, 1H), 5.04–4.98 (m, 1H), 4.95–4.87 (m, 1H), 4.31–4.07 (m, 6H), 4.01–3.86 (m, 1H), 3.37–3.30 (m, 1H), 3.23–3.03 (m, 1H), 2.71–2.63 (m, 1H), 1.46, 1.42 (2s, 9H), 1.37 (t, *J*=7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 171.2, 170.9, 151.2, 151.0, 130.3, 130.1, 126.1, 126.0, 125.1, 125.0, 124.9 (2C), 104.7, 80.3, 65.9, 65.8, 64.9, 64.8 (2C), 58.2, 57.8, 39.9, 39.5, 36.3, 34.8, 28.2, 28.1, 16.1, 16.0, 15.9; EIMS *m/z* (intensity) 433 ($[M+H]^+$, 12), 432 (M^+, 50), 359 (30), 239 (100), 155 (69); HRMS (EI) *m/z* calcd for $C_{18}H_{29}N_2O_8P$ 432.1662, found 432.1656.

4.1.6. 8-Oxo-4-oxa-7,12-diazatricyclo[7.2.1.0^{00}]dodeca-2,10-diene-12-carboxlic acid *tert*-butyl ester (15). $Pd(OAc)_2$ (3.1 mg, 0.014 mmol), dppp (11.4 mg, 0.028 mmol), and K_2CO_3 (19.2 mg, 0.139 mmol) were added to a solution of **14** (30 mg, 0.069 mmol) in THF (360 μL). This mixture was deoxygenated using freeze thaw cycles under vacuum and heated to 80 °C for 13 h. After cooling to rt, the mixture was diluted with brine (5 mL) and extracted with EtOAc (20 mL×2). The combined organic extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1 to 1:1) to afford **15** (6 mg, 31%) as a colorless oil: IR (neat) 3400, 2978, 2935, 2975, 1705, 1459, 1379, 1311, 1284, 1165, 1111, 1044 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.35 (dd, *J*=5.6, 2.4 Hz, 1H), 6.25 (dd, *J*=5.6, 2.4 Hz, 1H), 5.98 (s, 1H), 4.88 (br s, 1H), 4.81 (d, *J*=2.1 Hz, 1H), 4.11–3.96 (m, 2H), 3.90–3.86 (m, 1H), 3.56–3.50 (m, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.3, 153.6, 132.2, 131.0, 124.5, 114.1, 81.5, 64.8, 64.3, 58.4, 38.9, 28.3; EIMS *m/z* (intensity) 279 ($[M+H]^+$, 5), 278 (M^+, 33), 222 (45), 150 (34), 93 (46), 57 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{18}N_2O_4$ 278.1267, found 278.1270.

4.1.7. 4-Formyl-2,3-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (17). To a solution of 4-formyl-2,3-dihydropyrrole-2-dicarboxylic acid 2-methyl ester **16**[14] (1.04 g, 6.70 mmol) in CH_2Cl_2 (30 mL) was added DMAP (82 mg, 0.67 mmol) and Boc_2O (1.61 g, 7.37 mmol). The reaction mixture was stirred at rt for 10 h and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3) to afford **17** (1.13 g, 66%) as a pale yellow oily (1:1) mixture of rotamers: IR (neat) 3094, 2981, 2951, 1753, 1727, 1662, 1609, 1415 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.57 (s, 1H), 7.63, 7.46 (2s, 1H), 4.79 (2dd, *J*=12.2, 4.6 Hz, 1H), 3.78 (s, 3H), 3.20 (app. t, *J*=15.1 Hz, 1H), 2.88 (2br dd, *J*=15.1, 4.6 Hz, 1H), 1.53, 1.47 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ 185.0, 170.6, 170.4, 150.0, 146.8, 146.5, 122.3, 122.1, 83.3, 83.0, 59.7, 59.1, 52.4, 31.2, 30.1, 27.8, 27.6, 27.3; EIMS *m/z* (intensity) 255 (M^+, 25), 155 (40), 96 (40), 57 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{17}NO_5$ 255.1107, found 255.1118.

4.1.8. 4-Hydroxymethyl-2,3-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester. A solution of aldehyde **17** (95 mg, 0.370 mmol) in CH_2Cl_2 (1.5 mL) was cooled to −78 °C, treated with solid $NaBH_4$ (30 mg, 0.740 mmol) and then methanol (700 μL) dropwise. The reaction mixture was warmed to 0 °C over a 2 h period, quenched with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1 to 1:1) to afford the corresponding alcohol (95 mg, 99%) as a clear oily (1:1) mixture of rotamers: IR (neat) 3434, 2977, 2866, 1754, 1704, 1479, 1419 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.63, 6.51 (2br s, 1H), 4.72, 4.64 (2dd, *J*=11.9, 5.2 Hz, 1H), 4.18 (app. s, 2H), 3.77 (s, 3H), 3.11 (app. q, *J*=14.9 Hz, 1H), 2.69 (dt, *J*=16.8, 4.9 Hz, 1H), 1.49, 1.43 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.2, 172.0, 151.2, 126.0, 125.8, 119.6, 119.4, 80.8, 58.7, 58.5, 58.1, 52.2, 52.0, 35.4, 34.3, 28.0, 27.9; EIMS *m/z* (intensity) 258 ($[M+H]^+$, 11), 257 (M^+, 75), 198

(50), 157 (62), 53 (100); HRMS (EI) *m/z* calcd for $C_{12}H_{19}NO_5$ 257.1263, found 257.1275.

4.1.9. 4-(*tert*-Butyldimethylsilanyloxymethyl)-2,3-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (18). To a solution of the above alcohol (1.54 g, 5.99 mmol) in CH_2Cl_2 (25 mL) was added triethylamine (3.30 mL, 24.0 mmol) and DMAP (1.5 mg, 1.2 mmol) followed by a solution of TBSCl (1.08 g, 7.18 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at rt for 10 h, diluted with CH_2Cl_2 (30 mL), and washed with brine. The organic layer was dried ($MgSO_4$), concentrated, and purified by chromatography on SiO_2 (hexanes/EtOAc, 8:2) to afford **18** (1.84 g, 83%) as a pale yellow oily (1:1) mixture of rotamers: IR (neat) 2954, 2931, 2858, 2887, 1758, 1712, 1419, 1369 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.55, 6.42 (2s, 1H), 4.70, 4.63 (2dd, J=11.9, 5.1 Hz, 1H), 4.18 (app. s, 2H), 3.76 (s, 3H), 3.15–3.00 (m, 1H), 2.60 (dt, J=18.5, 4.8 Hz, 1H), 1.48, 1.43 (2s, 9H), 0.9, 0.89 (2s, 9H), 0.07, 0.06 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 172.0, 171.7, 151.1, 151.0, 125.4, 125.1, 119.2 (two peaks), 80.5, 80.3, 59.3, 58.6, 58.0, 52.0, 51.8, 35.4, 34.3, 28.0, 27.8, 25.6, 18.0, −5.6; EIMS *m/z* (intensity) 371 (M^+, 10), 271 (35), 228 (35), 80 (57), 75 (65), 57 (100); HRMS (EI) *m/z* calcd for $C_{18}H_{33}NO_5Si$ 371.2128, found 371.2136.

4.1.10. 4-(*tert*-Butyldimethylsilanyloxymethyl)-2,3-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester (19). To a solution of ester **18** (570 mg, 1.53 mmol) in methanol (8 mL) was added LiOH (78 mg, 1.84 mmol) at 0 °C, followed by H_2O (1.5 mL). The solution was warmed to rt, stirred for 10 h, concentrated, redissolved in H_2O (10 mL), acidified to pH 2–4 with 1 N HCl, and extracted with Et_2O (10 mL×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 3:1) to afford **19** (350 mg, 68%) as a clear oily mixture of rotamers: IR (neat) 2955, 2931, 2858, 1712, 1421, 1392, 1368, 1251, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.56, 6.36 (2s, 1H), 4.76, 4.65 (2dd, J=11.3, 5.4 Hz, 1H), 4.20 (app. s, 2H), 3.19–2.58 (m, 2H), 1.50, 1.44 (2s, 9H), 0.91, 0.90 (2s, 9H), 0.08, 0.07 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 176.7, 175.5, 152.1, 151.3, 125.3, 125.0, 120.3, 119.5, 81.5, 81.1, 59.5, 58.5, 58.2, 35.5, 34.0, 28.1, 28.0, 25.7, 25.5, 18.2, −3.9, −5.6; EIMS *m/z* (intensity) 357 (M^+, 10), 312 (10), 255 (15), 180 (15), 82 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{31}NO_5Si$ 357.1972, found 357.1964.

4.1.11. 4-(*tert*-Butyldimethylsilanyloxymethyl)-2-(ethoxycarbonylmethylmethylcarbamoyl)-2,3-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (20). To a solution of ester **18** (1 g, 3.01 mmol) in MeOH (15 mL) was added LiOH (190 mg, 4.52 mmol) followed by H_2O (3 mL) at 0 °C. The reaction mixture was stirred at rt for 10 h, concentrated, and partitioned between water (15 mL) and Et_2O (15 mL). The aqueous layer was acidified to pH 2–4 with 3 N HCl (~1.7 mL) and extracted with Et_2O (30 mL×2). The combined extracts were dried ($MgSO_4$) and concentrated to give the crude acid (804 mg). To a solution of this acid (804 mg, 3.01 mmol), sarcosine ethyl ester hydrochloride (461 mg, 3.01 mmol) and HOBt (4.05 mg, 3.01 mmol) in CH_2Cl_2 (10 mL) was added a solution of DCC (743 mg, 3.6 mmol) in CH_2Cl_2 (5 mL) at −10 °C. After 20 min, NEt_3 (1.25 mL, 9.09 mmol) was added. The reaction mixture was warmed to rt and stirred for 12 h, diluted with EtOAc (40 mL), and filtered. The solid was washed with EtOAc (5 mL). The combined filtrates were concentrated and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3) to afford **20** (734 mg, 54%) as a colorless glassy mixture of rotamers: IR (neat) 2955, 2930, 2857, 1749, 1705, 1669, 1423, 1366 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60, 6.48 (2s, 1H), 5.02, 4.94 (2dd, J=11.9, 5.3 Hz, 1H), 4.84–4.66 (m, 1H), 4.29–4.11 (m, 4H), 4.01, 3.53 (2d, J=17.3 Hz, 1H), 3.19–3.01 (m, 4H), 2.62–2.53 (m, 1H), 1.47, 1.43 (2s, 9H), 1.33–1.25 (m, 3H), 0.90, 0.89 (2s, 9H), 0.07, 0.06 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.4, 171.0, 168.9, 168.7, 151.2, 126.1, 126.0, 125.7, 119.5, 118.8, 118.6, 80.3, 61.3, 60.8, 59.6, 57.0, 56.2, 51.3, 49.6, 49.5, 35.8, 35.7, 35.4, 35.2, 34.9, 34.0, 28.1, 27.9, 25.7, 18.1, 13.9, −5.5; EIMS *m/z* (intensity) 456 (M^+, 25), 356 (45), 299 (35), 80 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{40}N_2O_6Si$ 456.2656, found 456.2652.

4.1.12. 2-{[1-*tert*-Butoxycarbonyl-4-(*tert*-butyldimethylsilanyloxymethyl)-2,3-dihydro-1*H*-pyrrole-2-carbonyl]-methylamino}malonic acid diethyl ester (21). A solution of **20** (200 mg, 0.438 mmol) in THF (4 mL) was added to a solution of LHMDS (1.05 mL, 1.05 mmol, 1 M in THF) in THF (2 mL) at −78 °C. After 10 min, ethyl chloroformate (101 μL, 1.05 mmol) was added dropwise. The reaction mixture was stirred for 2 h at the same temperature and then quenched with a saturated aqueous NH_4Cl solution (5 mL) at this temperature. The mixture was warmed to rt and partitioned between water (10 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3) to afford **21** (221 mg, 95%) as a colorless glassy mixture of rotamers: IR (neat) 2980, 2962, 2934, 2851, 1740, 1703, 1670, 1487, 1421, 1367 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60, 6.47 (2br s, 1H), 5.98, 5.91 (2s, 1H), 5.03, 4.96 (2d, J=11.9, 5.2 Hz, 1H), 4.34–4.10 (m, 6H), 3.23–3.04 (m, 4H), 2.58–2.48 (m, 1H), 1.47, 1.41 (2s, 9H), 1.36–1.24 (m, 3H), 0.89, 0.88 (2s, 9H), 0.06, 0.05 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.7, 171.5, 166.2, 166.2, 166.1, 165.9, 151.1, 151.1, 126.2, 125.9, 118.6, 80.4, 80.3, 61.8, 61.8, 60.2, 60.0, 59.5, 56.9, 56.4, 35.0, 34.1, 32.9, 32.7, 32.1, 31.2, 28.1, 27.8, 25.6, 18.1, 18.0, 13.8, −5.5; EIMS *m/z* (intensity) 528 (M^+, 7), 428 (45), 212 (66), 154 (83), 80 (100); HRMS (EI) *m/z* calcd for $C_{25}H_{44}N_2O_8Si$ 528.2867, found 528.2866.

4.1.13. 2-{[1-*tert*-Benzoyloxymethyl-l-*tert*-butoxycarbonyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl]methylamino}malonic acid diethyl ester (22b). To a solution of **21** (221 mg, 0.420 mmol) in THF (5 mL) was added TBAF (840 μL, 0.840 mmol, 1.0 M in THF) at 0 °C. The reaction mixture was slowly warmed to rt, stirred for 10 h, and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 2:8 to 1:9) to afford the alcohol (167 mg, 96%) as a colorless oil.

To a solution of this alcohol (167 mg) in CH_2Cl_2 (4 mL) was added DMAP (10 mg, 0.081 mmol), pyridine (130 μL, 1.61 mmol), and benzoyl chloride (94 μL, 0.81 mmol) at 0 °C. The reaction mixture was warmed to rt, stirred for

14 h, and diluted with CH_2Cl_2. The solution was washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 8:2 to 6.5:3.5) to afford **22b** (154 mg, 74%) as a colorless glassy mixture of rotamers: IR (neat) 2980, 2937, 1740, 1717, 1676, 1422, 1369 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12–8.09, 8.03–8.00 (2m, 2H), 7.63–7.53 (m, 1H), 7.50–7.40 (m, 2H), 6.86, 6.72 (2s, 1H), 5.96–5.89 (2s, 1H), 5.08, 5.02 (2d, J=11.9, 5.0 Hz, 1H), 4.94–4.79 (m, 2H), 4.31–4.18 (m, 4H), 3.32–3.02 (m, 4H), 2.68 (dd, J=16.0, 5.0 Hz, 1H), 1.48, 1.42 (2s, 9H), 1.33–1.23 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 171.7, 171.4, 166.4, 166.3, 166.2 (2C), 151.2 (2C), 133.5, 133.0, 130.5, 130.1, 130.0, 129.6, 128.4, 128.3, 113.2, 113.1, 81.2, 81.1, 62.1, 62.0, 61.2, 60.5, 57.2, 56.8, 35.8, 34.8, 33.1, 33.0, 28.3, 28.2, 28.0, 14.0; ESIMS m/z (intensity) 542 ([M+H]$^+$, 15), 541 (M$^+$, 60), 451 (45), 437 (100), 319 (60), 297 (85); HRMS (ESI) m/z calcd for $C_{26}H_{34}N_2O_9Na$ 541.2162, found 541.2180.

4.1.14. 2-{[l-*tert*-Butoxycarbonyl-4-(2,2-dimethylpropionyloxymethyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl]-methylamino}malonic acid diethyl ester (22c). To a solution of **21** (256 mg, 0.484 mmol) in THF (6 mL) was added TBAF (968 μL, 0.968 mmol, 1.0 M in THF) at 0 °C. The reaction mixture was slowly warmed to rt, stirred for 10 h, and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 2:8 to EtOAc) to afford the alcohol (197 mg, 96%) as a colorless oil.

To a solution of this alcohol (197 mg) in CH_2Cl_2 (5 mL) was added DMAP (5.8 mg, 0.048 mmol), pyridine (95 μL 1.9 mmol), and pivaloyl chloride (117 μL, 0.95 mmol) at 0 °C. The reaction mixture was warmed to rt, stirred for 14 h, and diluted with CH_2Cl_2. The product portion was washed with a saturated aqueous NH_4Cl solution, dried ($MgSO_4$), concentrated, and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 8:2 to 7:3) to afford **22c** (170 mg, 72%) as a colorless glassy mixture of rotamers: IR (neat) 2978, 2937, 2974, 1737, 1715, 1675, 1485, 1414 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.75, 6.62 (2s, 1H), 5.96, 5.89 (2s, 1H), 5.05, 4.98 (2dd, J=11.9, 4.9 Hz, 1H), 4.67–4.55 (m, 2H), 4.34–4.19 (m, 4H), 3.17, 3.14 (2s, 3H), 3.07 (d, J=15.9 Hz, 1H), 2.58 (dd, J=15.9, 4.7 Hz, 1H), 1.48, 1.45 (2s, 9H), 1.33–1.28 (m, 6H), 1.20, 1.19 (2s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.0, 171.4, 171.2, 166.1, 166.0, 165.9, 165.8, 150.9, 150.8, 129.5, 129.2, 113.4, 113.3, 80.8, 61.9, 60.3, 60.0, 56.9, 56.5, 38.5, 35.4, 34.4, 32.9, 32.7, 28.0, 27.8, 26.9, 13.8; ESIMS m/z (intensity) 522 ([M+H]$^+$, 31), 521 (M$^+$, 100); HRMS (ESI) m/z calcd for $C_{24}H_{38}N_2O_9Na$ 521.2475, found 521.2476.

4.1.15. 8-(3,3-Dimethylbutyryl)-3-methylene-4-oxo-3,8-diazabicyclo[3.2.1]octane-2,2-dicarboxylic acid diethyl ester (23). *Table 2, entry 1*: to a suspension of NaH (4 mg, 0.1 mmol) in THF (1 mL) was added a solution of **22b** (35 mg, 0.068 mmol) in THF (2.4 mL) at 0 °C. After stirring for 15 min at rt, the Pd-catalyst, preformed for 1 h at rt from $Pd(OAc)_2$ (1.5 mg, 6.8×10^{-3} mmol) and dppe (5.4 mg, 1.4×10^{-2} mmol) in THF (1 mL), was added, and the reaction mixture was heated at 65–70 °C for 1 h. After cooling to 0 °C, the reaction mixture was quenched with a saturated NH_4Cl solution and extracted with EtOAc (20 mL×2). The combined organic extracts were dried ($MgSO_4$), concentrated, and purified by chromatography on SiO_2 (hexanes/EtOAc, 1:1) to afford **23** (18 mg, 67%) as a colorless glassy solid: IR (neat) 2981, 2936, 1749, 1708, 1682, 1478, 1368 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.45 (br s, 1H), 5.15 (br s, 2H), 4.70 (br d, J=5.8 Hz, 1H), 4.38–4.16 (m, 4H), 2.97 (s, 3H), 2.75–2.60 (m, 2H), 1.44 (s, 9H), 1.33 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.8, 166.0, 165.3, 152.4, 142.1, 112.3, 81.3, 76.3, 62.9, 62.4, 58.9 (br), 36.8, 34.3, 28.1, 13.9; EIMS m/z (intensity) 396 (M$^+$, 10), 296 (41), 190 (85), 57 (100); HRMS (EI) m/z calcd for $C_{19}H_{28}N_2O_7$ 396.1897, found 396.1895.

Table 2, entry 5: to a solution of **22c** (45 mg, 0.09 mmol) in THF (3 mL) were added DBU (21 μL, 0.14 mmol) and a solution of $Pd(PPh_3)_4$ (10.4 mg, 9.03×10^{-3} mmol) in THF (1.5 mL). The reaction mixture was heated at 65–75 °C for 4 h, cooled to rt, and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3) to afford **23** (34 mg, 95%) as a colorless glassy solid.

Table 2, entry 6: to a solution of **22c** (36 mg, 0.072 mmol) in THF (3 mL) were added DBU (16 μL, 0.108 mmol) and a solution of Pd_2dba_3 (6.6 mg, 7.2×10^{-3} mmol) in THF (1 mL). The reaction mixture was heated at 65–75 °C for 2 h, cooled to rt, and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 7:3) to afford **23** (29 mg, 98%) as a colorless glassy solid.

4.2. General procedure A for the coupling of acid 19 and amines (24a and 24b)

4.2.1. 2-(Benzylethoxycarbonylmethylcarbamoyl)-4-(*tert*-butyldimethylsilanyloxymethyl)-2,3-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (25a). To a solution of acid **19** (123 mg, 0.369 mmol), *N*-benzylglycine ethyl ester hydrochloride (170 mg, 0.738 mmol), and 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (170 mg, 0.554 mmol) in CH_2Cl_2 (3.7 mL) was added triethylamine (205 μL, 1.48 mmol) dropwise at 0 °C. The solution was warmed to rt and stirred for 4 h. Saturated aqueous NaCl (5 mL) was added and the mixture was extracted with EtOAc (5 mL×3). The combined organic layers were washed with 1 N HCl, 5% Na_2CO_3, H_2O, and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 8:1 to 4:1) to afford **25a** (153 mg, 78%) as a clear oily mixture of rotamers: IR (neat) 2955, 2930, 2857, 1748, 1706, 1674, 1421 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.28 (m, 5H), 6.62, 6.47 (2s, 1H), 5.13–4.66 (m, 2H), 4.61–4.29 (m, 2H), 4.24–4.11 (m, 4H), 3.87–3.54 (m, 1H), 3.13–2.90 (m, 1H), 2.66 (dt, J=16.6, 4.8 Hz, 1H), 1.48 (s, 9H), 1.28–1.22 (m, 3H), 0.92–0.89 (m, 9H), 0.11–0.05 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 171.5, 168.9, 168.7, 151.3, 151.2, 136.2, 135.6, 128.7, 128.4, 128.3, 127.9 (2C), 127.1, 126.9, 118.7, 118.4, 80.6, 80.2, 59.5, 57.2, 56.6, 51.6, 51.3, 47.1, 47.0, 36.2, 35.9, 35.2, 34.6, 28.1 (2C), 25.7, 18.1, 13.9, −5.54; ESIMS m/z (intensity) 1087 ([2M+Na]$^+$, 15), 555 ([M+Na]$^+$, 100); HRMS (ESI) m/z calcd for $C_{28}H_{44}N_2NaO_6Si$ (M+Na) 555.2866, found 555.2826.

4.2.2. 4-(*tert*-Butyldimethylsilanyloxymethyl)-2-[(2,5-dimethoxybenzyl)ethoxycarbonylmethylcarbamoyl]-2,3-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (25b). According to general procedure A, acid **19** (70 mg,

0.210 mmol), *N*-(2,5-dimethoxy)benzylglycine ethyl ester[17] **24b** (59 mg, 0.231 mmol), 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (69 mg, 0.231 mmol), and triethylamine (60 μL, 0.420 mmol) afforded ester **25b** (80 mg, 64%) as a pale yellow oily (2.2:1) mixture of rotamers: IR (neat) 2955, 2931, 2856, 1748, 1705, 1674, 1502, 1463, 1421, 1391, 1366, 1279, 1250, 1224, 1166, 1114 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.03 (s, 1H), 6.83–6.75 (m, 2H), 6.59, 6.47 (2br s, 1H), 5.06, 4.94 (2dd, J=11.9, 5.5 Hz, 1H), 4.61–4.44 (m, 3H), 4.30–4.10 (m, 5H), 3.95–3.48 (m, 7H), 3.10–2.86 (m, 1H), 2.73–2.60 (m, 1H), 1.45, 1.43 (2s, 9H), 1.29–1.22 (m, 3H), 0.89, 0.88 (2s, 9H), 0.06, 0.04 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.9, 171.4, 169.0, 168.9, 153.7, 153.5, 151.4 (2C), 151.0, 126.3, 126.2, 124.9, 124.3, 119.7, 119.1, 118.5 (2C), 114.0, 113.7, 111.0, 110.8, 80.5, 80.0, 61.2, 60.7, 59.6, 56.8, 56.4, 55.5, 55.4, 49.2, 48.7, 47.2, 46.9, 36.0, 34.6, 28.1, 28.0, 25.7, 18.1, 13.9, −5.5; ESIMS *m/z* (intensity) 1207 ([2M+Na]$^+$, 85), 615 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calculated for $C_{30}H_{48}N_2NaO_8Si$ (M+Na) 615.3078, found 615.3049.

4.3. General procedure B for the C-acylations of esters 25a and 25b with ethyl chloroformate

4.3.1. 2-{Benzyl[1-*tert*-butoxycarbonyl-4-(*tert*-butyldimethylsilanyloxymethyl)-2,3-dihydro-1*H*-pyrrole-2-carbonyl]amino}malonic acid diethyl ester (26a). To a solution of ester **25a** (270 mg, 0.507 mmol) in Et_2O (5 mL) was added freshly prepared LHMDS (3.00 mL, 3.04 mmol, 1 M in THF) dropwise at −78 °C. After stirring for 1 h at this temperature, ethyl chloroformate (290 μL, 3.04 mmol) was added dropwise. The reaction mixture was stirred for 7 h at −78 °C and then quenched with saturated aqueous NH_4Cl (5 mL) at this temperature. The mixture was warmed to rt and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography on SiO_2 (hexanes/EtOAc, 8:1 to 4:1) to afford **26a** (233 mg, 76%) as a clear oily mixture of rotamers: IR (neat) 2956, 2930, 2857, 1742, 1706, 1462, 1421 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44–7.30 (m, 5H), 6.59, 6.43 (2s, 1H), 5.46, 5.40 (2s, 1H), 4.91–4.61 (m, 3H), 4.29–4.00 (m, 5H), 3.91–3.78 (m, 1H), 2.99, 2.81 (2app. t, J=13.9 Hz, 1H), 2.68, 2.57 (2dd, J=15.8, 4.8 Hz, 1H), 1.52, 1.47 (2s, 9H), 1.27, 1.25 (2t, J=7.1 Hz, 3H), 1.15, 1.13 (2t, J=7.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 172.7, 172.4, 166.1, 166.0, 165.9, 165.8, 151.4, 151.1, 136.2, 135.9, 128.5, 127.8, 127.5, 126.8 (2C), 126.5, 126.3, 118.6, 118.3, 81.1, 80.3, 61.9, 61.8, 61.4, 61.2, 59.6, 57.3, 56.7, 50.5, 50.3, 36.1, 34.8, 28.2, 25.8, 18.2, 13.8 (two peaks), 13.6, −5.4; ESIMS *m/z* (intensity) 1232 ([2M+Na]$^+$, 50), 628 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{31}H_{48}N_2NaO_8Si$ (M+Na) 627.3078, found 627.3078.

4.3.2. 2-{[1-*tert*-Butoxycarbonyl-4-(*tert*-butyldimethylsilanyloxymethyl)-2,3-dihydro-1*H*-pyrrole-2-carbonyl]-(2,5-dimethoxybenzyl)amino}malonic acid diethyl ester (26b). According to general procedure B, ester **25b** (550 mg, 0.927 mmol), LHMDS (6.5 mL, 6.49 mmol), and ethyl chloroformate (620 μL, 6.49 mmol) afforded **26b** (540 mg, 88%) as a clear foamy mixture of rotamers: IR (neat) 2955, 2932, 2856, 1742, 1705, 1501, 1464, 1421, 1391, 1301, 1281, 1251, 1266, 1223, 1165, 1114 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28, 7.10 (2s, 1H), 6.81–6.75 (m, 2H), 6.57, 6.43 (2s, 1H), 5.30, 5.23 (2s, 1H), 4.91–4.56 (m, 3H), 4.23–4.03 (m, 5H), 3.86 (s, 2H), 3.80, 3.79 (2s, 3H), 3.75 (s, 2H), 2.98 (app. t, J=11.9 Hz, 1H), 2.65 (dt, J=18.1, 4.5 Hz, 1H), 1.50, 1.44 (2s, 9H), 1.28–1.10 (m, 6H), 0.89, 0.88 (2br s, 9H), 0.05, 0.04 (2s, 6H); ^{13}C NMR ($CDCl_3$) δ 172.6, 172.3, 165.9, 165.7, 165.6, 165.5, 153.6, 151.3, 150.8, 150.4, 150.3, 126.2, 125.1, 124.6, 118.4, 118.3, 114.7, 114.2, 112.7, 111.9, 110.8, 110.6, 80.9, 80.0, 62.1, 61.7, 59.5, 56.7, 56.5, 55.6, 55.4, 45.8, 36.2, 34.3, 28.1, 28.0, 25.6, 18.0, 13.7, 13.6, 13.4, −5.6 (two peaks); ESIMS *m/z* (intensity) 1351 ([2M+Na]$^+$, 65), 687 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{33}H_{52}N_2NaO_{10}Si$ (M+Na) 687.3289, found 687.3286.

4.4. General procedure C for the TBS-deprotection of malonates 26a and 26b

4.4.1. 2-[Benzyl-(1-*tert*-butoxycarbonyl-4-hydroxymethyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl)amino]-malonic acid diethyl ester (27a). Malonate **26a** (100 mg, 0.165 mmol) was dissolved in THF (2 mL), cooled to 0 °C, and treated with TBAF (330 μL, 0.330 mmol, 1.0 M in THF). The solution was warmed to rt, stirred for 10 h, quenched with H_2O, and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1) to afford **27a** (74 mg, 92%) as a clear oily mixture of rotamers: IR (neat) 3468, 2980, 2934, 1741, 1702, 1497, 1421 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44–7.31 (m, 5H), 6.68, 6.53 (2s, 1H), 5.38, 5.34 (2s, 1H), 4.95–4.84 (m, 1H), 4.81–4.61 (m, 2H), 4.27–4.04 (m, 5H), 3.93–3.84 (m, 1H), 3.09–2.68 (m, 2H), 1.53, 1.48 (2s, 9H), 1.27, 1.25 (2t, J=7.1 Hz, 3H), 1.15 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.8, 172.5, 166.0, 165.9, 165.8, 151.5, 151.2, 136.0, 135.8, 128.6, 127.9, 127.6, 127.3, 126.9, 126.8, 118.6, 118.3, 81.3, 80.6, 62.0, 61.6, 61.5, 59.0 (2C), 57.4, 56.7, 50.5, 36.1, 34.7, 28.3, 28.2, 13.8 (2C), 13.7; ESIMS *m/z* (intensity) 1003 ([2M+Na]$^+$, 65), 985 (100), 513 ([M+Na]$^+$, 40); HRMS (ESI) *m/z* calcd for $C_{25}H_{34}N_2NaO_8$ (M+Na) 513.2213, found 513.2228.

4.4.2. 2-[(1-*tert*-Butoxycarbonyl-4-hydroxymethyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl)-(2,5-dimethoxybenzyl)-amino]malonic acid diethyl ester (27b). According to general procedure C, malonate **26b** (540 mg, 0.810 mmol) and TBAF (1.6 mL, 1.62 mmol) afforded alcohol **27b** (396 mg, 89%) as a clear foamy mixture of rotamers: IR (neat) 3479, 2978, 2837, 1741, 1702, 1501, 1465, 1420, 1391, 1368, 1301, 1282, 1223, 1178, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26, 7.11 (2s, 1H), 6.84–6.76 (m, 2H), 6.67, 6.52 (2s, 1H), 5.21, 5.12 (2s, 1H), 4.93–4.54 (m, 3H), 4.32–4.08 (m, 5H), 3.86 (s, 2H), 3.80 (s, 3H), 3.74 (s, 2H), 3.02 (app. t, J=13.8 Hz, 1H), 2.88–2.74 (m, 1H), 1.50, 1.45 (2s, 9H), 1.28–1.12 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 172.4, 172.3, 165.5, 165.4, 165.3, 153.5, 151.2, 150.7, 150.4, 150.3, 126.7, 126.5, 124.8, 124.3, 118.6, 114.6, 114.2, 112.8, 112.1, 110.7, 110.6, 80.9, 80.0, 62.1, 61.7, 61.6, 58.4, 56.7, 56.5, 55.4, 55.3, 45.9, 35.9, 34.3, 27.9, 27.8, 13.5, 13.4, 13.3; ESIMS *m/z* (intensity) 1123 ([2M+Na]$^+$, 35), 573 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{27}H_{38}N_2NaO_{10}$ (M+Na) 573.2424, found 573.2433.

4.5. General procedure D for the O-benzylation of alcohols 27a and 27b

4.5.1. 2-[(4-Benzoyloxymethyl-1-*tert*-butoxycarbonyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl)benzylamino]-malonic acid diethyl ester (28a). A solution of alcohol **27a** (375 mg, 0.765 mmol) and DMAP (9.3 mg, 0.0765 mmol) in CH_2Cl_2 (8 mL) was cooled to 0 °C and treated with pyridine (250 μL, 3.06 mmol) followed by benzoyl chloride (178 μL, 1.53 mmol). The solution was warmed to rt, stirred for 3 h, quenched with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography on SiO_2 (hexanes/EtOAc, 5:1 to 2:1) to afford **28a** (346 mg, 76%) as a clear oily (6.7:1) mixture of rotamers: IR (neat) 2980, 1713, 1452, 1418, 1368, 1269, 1107, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (d, J=8.1 Hz, 2H), 7.55 (t, J=7.4 Hz, 1H), 7.45–7.29 (m, 7H), 6.85, 6.69 (2s, 1H), 5.37, 5.35 (2s, 1H), 4.97–4.57 (m, 5H), 4.28–4.00 (m, 3H), 3.90–3.76 (m, 1H), 3.15–2.75 (m, 2H), 1.53, 1.49 (2s, 9H), 1.25, 1.23 (2t, J=7.1 Hz, 3H), 1.12 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.3, 172.0, 166.4, 166.1, 165.9, 165.8, 151.4, 151.0, 135.9, 135.7, 132.9, 130.5, 130.1, 130.0, 129.6, 128.7, 128.4, 128.3, 127.9, 127.6, 126.8, 126.7, 113.1, 112.8, 81.6, 81.0, 62.1, 62.0, 61.5, 61.4, 61.2 (two peaks), 57.5, 56.9, 50.5, 50.4, 36.5, 35.2, 28.3, 28.2, 13.9, 13.8, 13.7; ESIMS m/z (intensity) 635 ([M+K]$^+$, 100), 617 ([M+Na]$^+$, 65); HRMS (ESI) m/z calcd for $C_{32}H_{38}N_2NaO_9$ (M+Na) 617.2475, found 617.2448.

4.5.2. 2-[(4-Benzoyloxymethyl-1-*tert*-butoxycarbonyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl)-(2,5-dimethoxybenzyl)amino]malonic acid diethyl ester (28b). According to general procedure D, alcohol **27b** (390 mg, 0.707 mmol), DMAP (9 mg, 0.0707 mmol), pyridine (63 μL, 0.778 mmol), and benzoyl chloride (165 μL, 1.41 mmol) afforded **28b** (320 mg, 70%) as a clear foamy (4.8:1) mixture of rotamers: IR (neat) 2979, 1712, 1681, 1501, 1451, 1392, 1368, 1318, 1270, 1223, 1163, 1108 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (d, J=7.5 Hz, 2H), 7.56 (t, J=6.8 Hz, 1H), 7.43 (app. t, J=7.5 Hz, 2H), 7.27 (s, 0.5H), 7.12 (s, 0.5H), 6.84 (s, 0.5H), 6.81–6.74 (m, 2H), 6.69 (s, 0.5H), 5.27, 5.14 (2s, 1H), 4.95–4.57 (m, 5H), 4.23–4.01 (m, 3H), 3.85 (s, 2H), 3.79 (s, 3H), 3.74 (s, 2H), 3.08 (app. t, J=13.8 Hz, 1H), 2.86 (dt, J=18.2, 4.7 Hz, 1H), 1.50, 1.47 (2s, 9H), 1.28–1.09 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 172.0, 171.8, 166.0, 165.6, 165.4, 165.3, 151.1, 150.4, 150.4, 150.2, 132.6, 130.1, 130.0, 129.7 (2C), 129.6, 129.2, 127.9, 124.7, 124.2, 114.6, 114.2, 112.8, 112.7, 112.6, 112.0, 110.7, 110.6, 81.1, 80.4, 62.2, 61.7, 61.6, 60.8, 56.9, 56.7, 55.4, 55.3, 45.9, 45.8, 36.4, 34.8, 27.9, 27.8, 13.6, 13.5, 13.3; ESIMS m/z (intensity) 1331 ([2M+Na]$^+$, 20), 677 ([M+Na]$^+$, 100); HRMS (ESI) m/z calcd for $C_{34}H_{42}N_2NaO_{11}$ (M+Na) 677.2686, found 677.2662.

4.6. General procedure E for the palladium-catalyzed allylic alkylation of malonates 28a and 28b

4.6.1. 3-Benzyl-7-methylene-4-oxo-3,8-diazabicyclo[3.2.1]-octane-2,2,8-tricarboxylic acid 8-*tert*-butyl ester 2,2-diethyl ester (29a). A suspension of malonate **28a** (50 mg, 0.084 mmol) and Pd_2dba_3 (15 mg, 0.0168 mmol) in degassed THF (4 mL) was cooled to −78 °C and treated with DBU (19 μL, 0.126 mmol). The reaction mixture was warmed to rt and then heated to 65 °C for 20 min. Upon cooling, the mixture was transferred to a short Celite column and washed with CH_2Cl_2 (10 mL). The eluant was concentrated and purified by chromatography on SiO_2 (hexanes/EtOAc, 5:1 to 1:1) to afford **29a** (38 mg, 96%) as a clear oil: IR (neat) 2981, 2935, 1748, 1690, 1392, 1368, 1310, 1254, 1166, 1107 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (dd, J=7.2, 7.2 Hz, 2H), 7.15 (t, J=7.2 Hz, 1H), 7.07 (d, J=7.2 Hz, 2H), 5.48 (br s, 1H), 5.24 (br s, 2H), 4.80–4.65 (m, 3H), 4.23–3.86 (m, 4H), 2.78–2.67 (m, 2H), 1.48 (s, 9H), 1.19 (t, J=7.2 Hz, 3H), 1.12 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.2, 166.0, 165.7, 152.7, 142.2, 137.8, 128.0, 126.3, 125.8, 112.8, 81.3, 75.8, 62.6, 62.3, 59.1, 49.7, 36.6, 28.2, 13.6, 13.5; ESIMS m/z (intensity) 967 ([2M+Na]$^+$, 100), 495 ([M+Na]$^+$, 75); HRMS (ESI) m/z calcd for $C_{25}H_{32}N_2NaO_7$ (M+Na) 495.2107, found 495.2088.

4.6.2. 2-[(4-Benzoyloxymethyl-1-*tert*-butoxycarbonyl-2,3-dihydro-1*H*-pyrrole-2-carbonyl)-(2,5-dimethoxybenzyl)amino]malonic acid diethyl ester (29b). According to general procedure E, malonate **28b** (310 mg, 0.473 mmol), Pd_2dba_3 (87 mg, 0.0946 mmol), and DBU (107 μL, 0.709 mmol) afforded **29b** (273 mg, 94%) as a clear foam: IR (neat) 2981, 2939, 1747, 1689, 1499, 1466, 1433, 1391, 1368, 1309, 1277, 1254, 1219, 1164, 1111, 1047 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.67–6.57 (m, 2H), 6.37 (d, J=2.7 Hz, 1H), 5.44 (br s, 1H), 5.22 (app. d, J=12.4 Hz, 2H), 4.78 (br d, J=5.2 Hz, 1H), 4.63, 4.59 (AB q, J=17.6 Hz, 2H), 4.15–3.73 (m, 4H), 3.69 (s, 3H), 3.62 (s, 3H), 2.79–2.62 (m, 2H), 1.48 (s, 9H), 1.11–1.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 169.9, 165.7, 165.3, 153.2, 152.4, 150.1, 142.0, 126.7, 112.7, 111.6, 111.5, 110.6, 81.0, 77.2, 75.6, 62.4, 62.1, 59.0, 55.4, 55.1, 44.9, 36.6, 28.0, 27.9, 13.3 (2C), 13.2; ESIMS m/z (intensity) 1087 ([2M+Na]$^+$, 100), 555 ([M+Na]$^+$, 72); HRMS (ESI) m/z calcd for $C_{27}H_{36}N_2NaO_9$ (M+Na) 555.2319, found 555.2314.

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