Weinreb Amide Based New Synthetic Equivalents for Convenient Access to Immunosuppressive Agent FTY720 and Analogues

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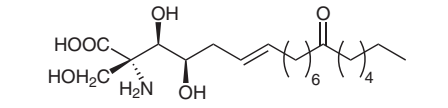
Received 3 August 2007

Dedicated to Professor Shoichi Kusumoto

Abstract: Three new synthetic equivalents containing Weinreb amide functionality for the central core of FTY720, an immunosuppressive agent, have been developed. These synthetic equivalents enabled incorporation of the polar head group of FTY720, through Julia, Wittig, and Horner–Wadsworth–Emmons reactions and also allowed for variation in the chain length of the lipophilic side chain in target, through the Weinreb amide functionality therein. The use of tris(hydroxymethyl)aminomethane, commercially available at low cost for the polar head group offers a distinct advantage. Convenient reactions and simple functional group interconversions in good to high yield highlight the strength of the new route developed for the synthesis of clinically important FTY720.

Key words: FTY720, Weinreb amide, sulfone, olefination

FTY720 (**1**, Figure 1) is a novel and promising immunosuppressant that is currently in phase III clinical trials for the prevention of allograft rejection.[1] It is a synthetic analogue of sphingosine ISP-I (myriocin), a fungal metabolite of Chinese herb *Iscaria sinclarri*.[2] The known synthetic schemes[3,4] for FTY720 start with octylbenzene,[3b,c] 4-octylbenzaldehyde,[3d,4b] 4-octyliodobenzene,[4a] or 2-(4-hydroxyphenyl)ethanol,[4c] as the starting building block. Fürstner's approach banking on the use of 2-(4-hydroxyphenyl) ethanol as the starting material has great potential in varying the lipophilic side chain with the use of environmentally benign $Fe(acac)_3$ during cross-coupling reaction between aryl triflate and alkylmagnesium halide. In contrast to acetaminomalonate, the use of tris(hydroxymethyl)aminomethane (TRIS), for incorporating the polar head group of FTY720, has been reported only recently.[4a]



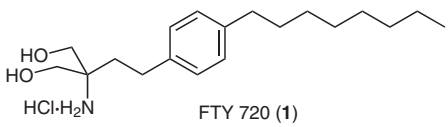


Figure 1

A new strategy based on a disconnection represented in Figure 2 was envisaged. The importance of the target, our continued interest in developing synthetic equivalents based on the Weinreb amide functionality,[5,6] increasing confidence of this functionality being used industrially on kilogram scale,[7] and the absence of a strategy based on the proposed disconnection herein were the main reasons justifying our synthetic efforts. The proposed synthetic scheme has two distinct and prominent advantages. Firstly, for the hydrophilic head group in FTY720, it envisages the use of *N*-Boc-protected aldehyde **2**,[8] conveniently prepared in two steps from inexpensive and commercially available tris(hydroxymethyl)aminomethane (TRIS, **3**) as the starting substrate.

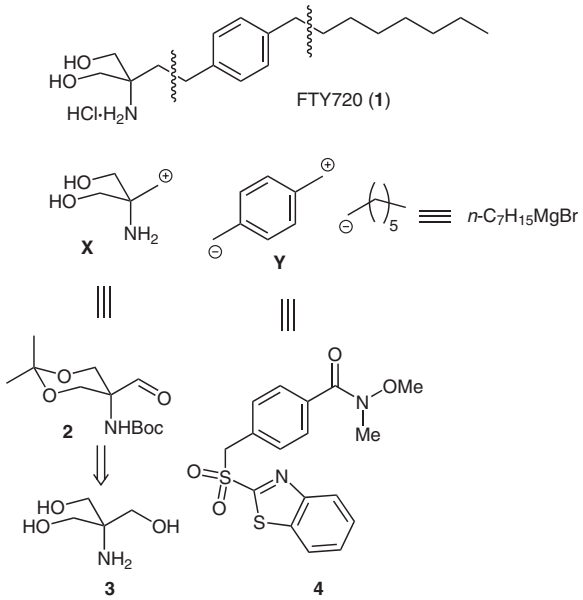
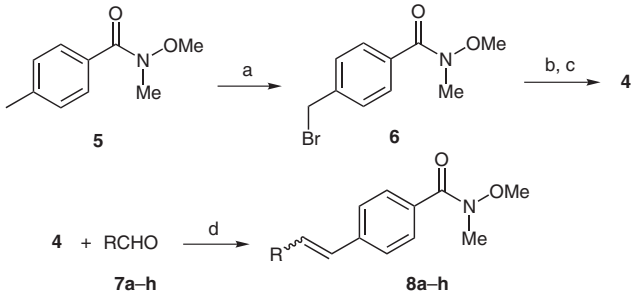


Figure 2

Secondly, it allows for convenient structural variations at the lipophilic side chain of FTY720 through a robust Weinreb amide functionality in the central building block **4** (Figure 2). The coupling of compound **4** with aldehyde **2** banks on the efficiency and success of Julia olefination protocol. The absence of compound **4** in the literature, which combines potentials of Julia olefination[9] and Weinreb amide chemistry, further prompted this investigation. Analytically pure compound **4**[10] was conveniently prepared in three steps using easily available amide **5**[11] as the

SYNLETT 2007, No. 18, pp 2841–2846
Advanced online publication: 19.10.2007
DOI: 10.1055/s-2007-990961; Art ID: G26607ST



Scheme 1 *Reagents and conditions*: (a) NBS (1.1 equiv), Bz_2O_2, CCl_4, reflux, 16 h, 62–65%; (b) 2-mercaptobenzothiazole (1.1 equiv), K_2CO_3 (1.5 equiv), acetone, reflux, 10 h, 60%; (c) $Na_2WO_4{\cdot}2H_2O$ (0.5 equiv), 30% H_2O_2 (4.0 equiv), MeOH, 0 °C to r.t., 6 h, 77%; (d) K_2CO_3 (3.0 equiv), THF–DMF (3:1), 70 °C, 17 h.

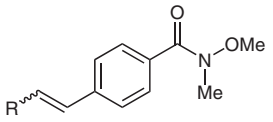
starting substrate (Scheme 1). It involved facile benzylic bromination followed by nucleophilic substitution with 2-mercaptobenzothiazole and oxidation of the resulting sulfide to sulfone **4**.

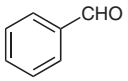
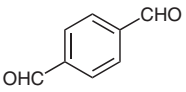
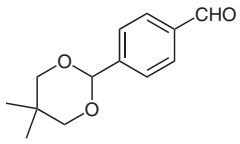
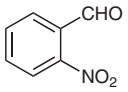
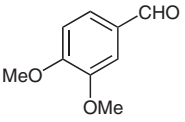
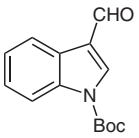
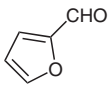
The successful use of Cs_2CO_3 as a base in the literature[12] for Julia olefination prompted the possible use of cheaper K_2CO_3, particularly in conjunction with DMF as an adjunct solvent. To our satisfaction, a variety of aldehydes cleanly reacted with the sulfone **4** in THF–DMF mixture (3:1) at 70 °C when three equivalents of K_2CO_3 were used as a base. The obtained alkenes **8a**–**h**[13] in moderate to good yields contained *E* as the major geometrical isomer (Table 1).

Towards the synthesis of FTY720, the sulfone **4** was then reacted with aldehyde **2** under similar reaction conditions. Clean reaction ensued furnishing the desired product **9**[14] after silica gel chromatography in an isolated yield of 55%. Realizing the importance of **9** as a key building block towards FTY720 and its analogues, attempts to increase the yield of this reaction were made. After a few variations in the nature of reaction solvent, it was observed that good yield of 70% was obtained when DMF alone was used as the solvent. The convenient availability of **9** and subsequent facile addition of alkylmagnesium halides of varying lengths, proves the importance of scaffold **9** as a key building block for FTY720 and the significance of the Weinreb amide functionality therein (Scheme 2). All the ketones, **10a**–**e**,[15] were obtained in moderate yields (Table 2).

Given the fact that arylmagnesium halides are prone to oxidative homodimerization as a parasitic side reaction under $Fe(acac)_3$-catalyzed cross-coupling reactions of Grignard reagents with electron-deficient aromatic substrates,[16] the successful addition of phenylmagnesium bromide and obtainment of ketone **10e**, substantiate the promise of this new strategy towards incorporation of the aryl residue in the lipophilic side chain for FTY720 analogues. With the facile conversion of **10d** to **11**,[4a] a formal total synthesis of target molecule FTY720 has been achieved. Compound **11** obtained in high yield of 85% over two steps from **10d** is an advanced and ultimate precursor in the recently reported synthesis of FTY720.[4a]

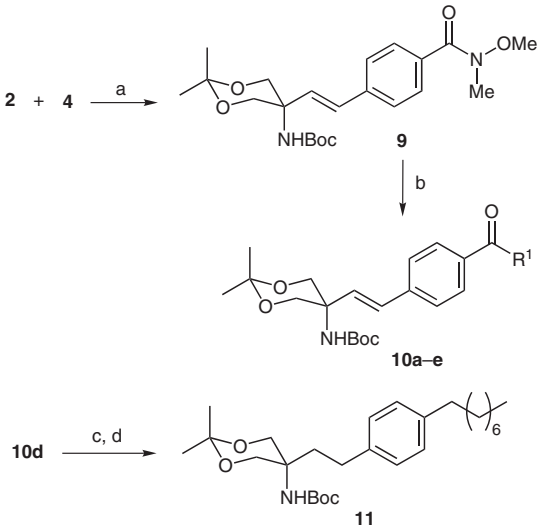
Table 1 Julia Olefination of Aldehydes **7a**–**h** with Sulfone **4**



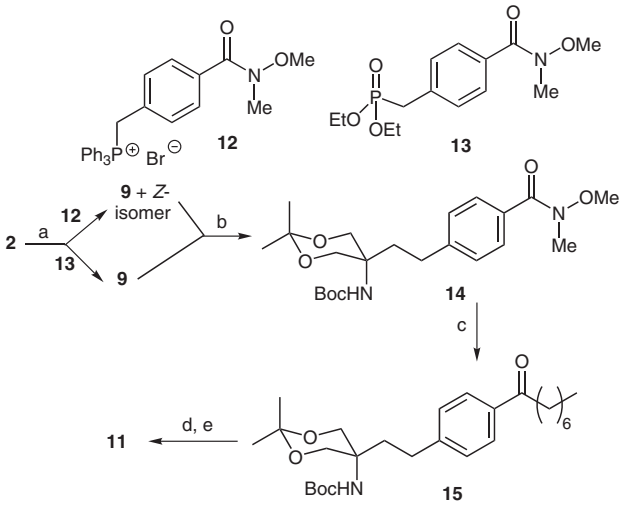
RCHO	Product (% yield,[a] *E*/*Z* ratio)
 **7a**	**8a** (72, 2:1)
 **7b**	**8b** (57, 9:1)
 **7c**	**8c** (64, 3:1)
 **7d**	**8d** (70, 9:1)
 **7e**	**8e** (66, 3:1)
 **7f**	**8f** (56, 3:2)
 **7g**	**8g** (75, 5:4)
n-Butyraldehyde **7h**	**8h**[b] (78, 2:1)

[a] Yield of isolated product after flash chromatography. All isolated new compounds exhibited satisfactory analytical and spectral details. The *E*/*Z* isomers were characterized using ^{1}H NMR.
[b] Reaction was carried out using NaH in DMF at 0 °C.

Successful coupling of the sulfone **4** with aldehyde **2** and the achieved synthesis of FTY720 hinted at the possible use of Wittig or Horner–Wadsworth–Emmons (HWE) based central units **12** and **13**, respectively. Interestingly, both of these compounds, although not in the literature, were easily prepared[17] using the bromo amide **6**. Heating of the Wittig salt **12** along with the aldehyde **2** in the presence of K_2CO_3 in THF–DMF mixture at 70 °C led to in



Scheme 2 *Reagents and conditions*: (a) K_2CO_3 (3.0 equiv), **2** (1.0 equiv), THF–DMF (3:1), 70 °C, 18 h, 55%; DMF, 70%; (b) R^1MgX (6.0 equiv), THF, –10 °C to 0 °C, 3 h; (c) $NaBH_4$ (3.0 equiv), MeOH, 0 °C, 2 h; (d) H_2, 10% Pd/C (30 wt%), EtOAc, AcOH (5 equiv), r.t., 24 h, 85% (2 steps).



Scheme 3 *Reagents and conditions*: (a) K_2CO_3 (3.0 equiv), **2** (1.0 equiv), THF–DMF (3:1), 70 °C, 18 h, 70% from **12** and 60% from **13**; (b) H_2, 10% Pd/C (25 wt%); EtOAc, r.t., 24 h, 95%; (c) *n*-$C_7H_{15}MgBr$ (6.0 equiv), THF, –10 °C to 0 °C, 3 h, 70%; (d) $NaBH_4$ (3.0 equiv), MeOH, 0–10 °C, 2 h; (e) H_2, 10% Pd/C (25 wt%); EtOAc, AcOH (5 equiv), r.t., 24 h, 90% (2 steps).

Table 2 Addition of Various Organometallic Reagents to Weinreb Amide **9**

Entry	R^1M	R^1 in the product (yield, %[a])	
1	$Me(CH_2)_3MgBr$	**10a**	$(CH_2)_3Me$ (70)
2	$Me(CH_2)_5MgBr$	**10b**	$(CH_2)_5Me$ (65)
3	$Me(CH_2)_7MgBr$	**10c**	$(CH_2)_7Me$ (68)
4	$Me(CH_2)_6MgBr$	**10d**	$(CH_2)_6Me$ (75)
5	PhMgBr	**10e**	Ph (72)

[a] Yield of isolated product after flash chromatography. All isolated new compounds exhibited satisfactory analytical and spectral details.

situ formation of the phosphorane and subsequent reaction with aldehyde **2**. The reaction furnished the desired product **9** along with the *Z*-isomer (*E*/*Z* = 3:1)[18] in an isolated yield of 70%. However, under similar reaction conditions the phosphonate **13** gave the *E*-isomer **9** as the exclusive product in 60% yield. Simple hydrogenation of the *E*/*Z* product mixture from the Wittig reaction and convergence to alkane amide **14**[19] makes the obtainment of geometrical isomers with building block **12** inconsequential. Compound **14**, a stable crystalline solid is yet another building block for the synthesis of FTY720 and analogues. Addition of *n*-$C_7H_{15}MgBr$, at –10 °C furnished the ketone **15**[20] in 70% yield. Finally, successful conversion of **15** to **11** in high yield demonstrates the usefulness of compound **14** as a key building block, not only for FTY720, but for its analogues as well (Scheme 3).

To conclude, a successful strategy for the synthesis of FTY720, an immunosuppressive agent based on an unexplored disconnection has been realized. For this, three new synthetic equivalents containing the Weinreb amide functionality for the central core of FTY720 have been developed from commercially available *p*-toluic acid. These synthetic equivalents enabled incorporation of the polar head group of FTY720, through Julia, Wittig, and HWE reactions and also allowed for complete control at the length of the lipophilic side chain through the robust amide functionality therein. All the reactions and conditions en-route to the target molecule are simple and good-yielding and therefore hold significant promise for industrial application.

Acknowledgment

We thank DST-New Delhi for the funding towards 400 MHz NMR machine to the Department of Chemistry, IIT-Madras under the IRPHA scheme and ESI-MS facility under the FIST program. CSIR-New Delhi is acknowledged for funding of project 01(1971)/05/EMR-II during 2005. B.S.R. is thankful to IIT-Madras for Fellowship, A.S.M. is thankful for a JRF Fellowship under the above project.

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(10) **4-{(Benzo[*d*]thiazol-2-ylsulfonyl)methyl}-*N*-methoxy-*N*-methylbenzamide (4)**
Yield 85–88%; R_f = 0.35 (hexane–ethyl acetate, 6:4); colorless crystals, mp 142–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.32 (s, 3 H), 3.47 (s, 3 H), 4.79 (s, 2 H), 7.33 (d, 2 H, *J* = 8.0 Hz), 7.56–7.62 (m, 3 H), 7.63–7.69 (m, 1 H), 7.94 (d, 1 H, *J* = 8.0 Hz), 8.26 (d, 1 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.6, 59.7, 60.1, 121.3, 124.6, 126.8, 127.2, 127.8, 127.9, 129.8, 133.9, 136.1, 151.6, 164.1, 168.0. IR (CH_2Cl_2): 1152, 1332, 1469, 1639, 2929, 2972 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{17}H_{16}N_2O_4S_2$ [M + H]$^+$: 377.0630; found: 377.0618.

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(13) **General Procedure for Olefination**
A suspension of sulfone (0.3 mmol), aldehyde (0.33 mmol, 1.1 equiv), and K_2CO_3 (0.9 mmol, 3 equiv) in a mixture of THF (1.8 mL) and DMF (0.6 mL; 3:1 mixture) was heated at 70 °C for 17 h. After completion of the reaction, THF was evaporated and the reaction mixture was quenched with H_2O and then extracted with EtOAc. The washed organic layer was dried over anhyd Na_2SO_4, filtered, concentrated, and then purified by silica gel flash chromatography. The spectral and analytical details for selected compounds are given below.

4-[4-(5,5-Dimethyl-1,3-dioxan-2-yl)styryl]-*N*-methoxy-*N*-methylbenzamide (8c)
Yield 64% (*E*:*Z* = 3:1). *E*-Isomer: R_f = 0.35 (hexane–EtOAc, 7:3); white crystalline solid, mp 121–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.73 (s, 3 H), 1.22 (s, 3 H), 3.28 (s, 3 H), 3.48 (s, 3 H), 3.58 (d, 2 H, *J* = 10.8 Hz), 3.70 (d, 2 H, *J* = 11.2 Hz), 5.32 (s, 1 H), 7.03 (d, 1 H, *J* = 16.0 Hz), 7.10 (d, 1 H, *J* = 16.4 Hz), 7.41–7.46 (m, 6 H), 7.62 (d, 2 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 22.0, 29.2, 32.8, 60.0, 76.7, 100.4, 125.0, 125.6, 127.1, 127.6, 127.8, 129.1, 131.9, 136.5, 137.2, 138.6, 168.5. *Z*-Isomer: R_f = 0.42 (hexane–EtOAc, 7:3); colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.27 (s, 3 H), 3.49 (s, 3 H), 3.57 (d, 2 H, *J* = 10.4 Hz), 3.69 (d, 2 H, *J* = 11.2 Hz), 5.28 (s, 1 H), 6.51 (d, 1 H, *J* = 12.4 Hz), 6.57 (d, 1 H, *J* = 12.4 Hz), 7.17–7.21 (m, 4 H), 7.30 (d, 2 H, *J* = 8.0 Hz), 7.46 (d, 2 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 22.1, 29.2, 33.0, 59.9, 76.7, 100.6, 125.2, 127.3, 127.5, 127.8, 128.6, 130.2, 131.6, 136.4, 136.6, 138.6, 168.7. IR (CH_2Cl_2): 1097, 1383, 1417, 1638, 2850, 2954 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{23}H_{27}NO_4$ [M + H]$^+$: 382.2018; found: 382.2029.

***N*-Methoxy-*N*-methyl-4-(2-nitrostyryl)benzamide (8d)**
Yield 70% (*E*:*Z* = 9:1); R_f = 0.4 (hexane–EtOAc,7:3); yellow solid, mp 60–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (*E*-isomer) = 3.38 (s, 3 H), 3.58 (s, 3 H), 7.09 (d, 1 H, *J* = 16.0 Hz), 7.42–7.46 (m, 1 H), 7.57 (d, 2 H, *J* = 8.4 Hz), 7.62 (d, 1 H, *J* = 7.6 Hz), 7.67 (d, 1 H, *J* = 16.4 Hz), 7.73 (d, 2 H, *J* = 8.4 Hz), 7.77 (d, 1 H, *J* = 7.2 Hz), 7.98–8.00 (m, 1 H); δ (*Z*-isomer, nonoverlapped signals) = 3.32 (s, 3 H), 3.52 (s, 3 H), 6.77 (d, 1 H, *J* = 12.0 Hz), 6.97 (d, 1 H, *J* = 12.0 Hz), 7.49 (d, 2 H, *J* = 8.0 Hz), 7.81 (d, 1 H, *J* = 8.0 Hz), 7.93 (d, 1 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*E*-isomer) = 33.2, 60.5, 124.4, 124.8, 126.1, 127.8, 127.9, 128.4, 132.2, 132.4, 132.7, 133.3, 138.2, 147.6, 168.8; δ (*Z*-isomer, nonoverlapped signals) = 60.6, 124.3, 128.2, 130.4, 131.7, 132.8. IR (CH_2Cl_2): 1264, 1345, 1523, 1635, 3054 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{17}H_{16}N_2O_4$ [M + H]$^+$: 313.1188; found: 313.1194.

4-(3,4-Dimethoxystyryl)-*N*-methoxy-*N*-methyl Benzamide (8e)
Yield 66% (*E*:*Z* = 3:1); R_f = 0.37 (hexane–EtOAc, 7:3); yellow viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (*E*-isomer) = 3.28 (s, 3 H), 3.49 (s, 3 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 6.78 (d, 1 H, *J* = 8.0 Hz), 6.89 (d, 1 H, *J* = 16.4 Hz), 6.97–6.99 (m, 2 H), 7.04 (d, 1 H, *J* = 16.0 Hz), 7.43 (d, 2 H, *J* = 8.4 Hz), 7.62 (d, 2 H, *J* = 8.4 Hz); δ (*Z*-isomer, nonoverlapped signals) = 3.26 (s, 3 H), 3.46 (s, 3 H), 3.54 (s, 3 H), 3.77 (s, 3 H), 6.43 (d, 1 H, *J* = 12.4 Hz), 6.51 (d, 1 H, *J* = 12.4 Hz), 6.65–6.68 (m, 2 H), 6.72–6.74 (m, 1 H), 7.24 (d, 2 H, *J* = 8.4 Hz), 7.47 (d, 2 H, *J* = 8.4 Hz). ^{13}C NMR (100

MHz, $CDCl_3$): δ = 33.8, 55.8, 55.9, 61.1, 108.8, 111.2, 120.3, 121.9, 125.7, 128.2, 128.5, 128.8, 130.2, 131.2, 132.3, 139.9, 149.1, 149.3, 169.5; δ (*Z*-isomer non-overlapped signals) = 55.5, 55.8, 60.9, 110.9, 111.7, 125.8, 127.9, 128.6, 129.4, 130.0, 140.2, 148.3, 148.4, 169.6. IR (CH_2Cl_2): 1264, 1514, 1635, 3053 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{19}H_{21}NO_4$ $[M + H]^+$: 328.1549; found: 328.1546.

***tert*-Butyl {3-[4-Methoxy(methyl)carbamoyl]styryl}-1*H*-indole-1-carboxylate (8f)**

Yield 56% (*E*:*Z* = 3:2); *Rf* = 0.27 (hexane–EtOAc, 7:3); pale yellow viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ (*E*-isomer) = 1.70 (s, 9 H), 3.38 (s, 3 H), 3.58 (s, 3 H), 7.21 (d, 1 H, *J* = 17.2 Hz), 7.32–7.38 (m, 4 H), 7.55 (d, 2 H, *J* = 8.4 Hz), 7.72 (d, 2 H, *J* = 8.4 Hz), 7.77 (s, 1 H), 7.90 (d, 1 H, *J* = 7.2 Hz), 8.20 (d, 1 H, *J* = 8.0 Hz); δ (*Z*-isomer, nonoverlapped signals) = 3.33 (s, 3 H), 3.52 (s, 3 H), 6.68–6.75 (m, 2 H), 7.08–7.12 (m, 1 H), 7.23–7.29 (m, 2 H), 7.35 (d, 2 H, *J* = 8.4 Hz), 7.48 (s, 1 H), 7.56 (d, 2 H, *J* = 8.4 Hz), 8.11 (d, 1 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*E*-isomer) = 28.2, 33.8, 61.1, 84.1, 115.5, 118.7, 119.9, 121.7, 123.1, 124.5, 124.8, 125.6, 127.8, 128.5, 128.9, 132.4, 140.1, 149.5, 169.6; δ (*Z*-isomer, nonoverlapped signals) = 83.8, 115.1, 117.0, 121.5, 122.5, 124.4, 128.3, 129.2, 130.4, 132.6, 135.2. IR (CH_2Cl_2): 1261, 1457, 1604, 1723, 2853, 2923, 2956 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{24}H_{26}N_2O_4$ $[M + H]^+$: 407.1971; found: 407.1981.

4-[2-(Furan-2-yl)vinyl]-*N*-methoxy-*N*-methyl Benzamide (8g)

Yield 75% (*E*:*Z* = 5:4); *Rf* = 0.3 (hexane–EtOAc, 7:3); yellow viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ (*E*-isomer) = 3.26 (s, 3 H), 3.46 (s, 3 H), 6.18–6.23 (m, 1 H), 6.29–6.37 (m, 4 H), 6.85 (d, 1 H, *J* = 16.0 Hz), 6.94 (d, 1 H, *J* = 16.4 Hz), 7.37–7.41 (m, 4 H), 7.56–7.60 (m, 3 H); δ (*Z*-isomer, nonoverlapped signals) = 3.27 (s, 3 H), 3.48 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*E*-isomer) = 33.8, 61.0, 109.5, 111.8, 118.0, 125.7, 126.0, 128.8, 132.6, 139.4, 142.5, 152.9, 169.5; δ (*Z*-isomer, nonoverlapped signals) = 110.7, 111.3, 118.9, 126.7, 128.1, 128.3, 139.8, 141.9, 151.7, 169.7. IR (CH_2Cl_2): 1378, 1416, 1639, 2929 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{15}H_{15}NO_3$ $[M + H]^+$: 258.1130; found: 258.1138.

(14) **(*E*)-*tert*-Butyl (5-{4-[Methoxy(methyl)carbamoyl]styryl}-2,2-dimethyl-1,3-dioxan-5-yl)carbamate (9)**

Yield 70%; R_f = 0.35 (hexane–EtOAc, 6:4); colorless solid, mp 115–118 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 9 H), 1.38 (s, 3 H), 1.40 (s, 3 H), 3.26 (s, 3 H), 3.45 (s, 3 H), 3.82–3.92 (m, 4 H), 5.27 (br s, 1 H), 6.23 (d, 1 H, *J* = 16.4 Hz), 6.48 (d, 1 H, *J* = 16.4 Hz), 7.30 (d, 2 H, *J* = 8.0 Hz), 7.56 (d, 2 H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 27.4, 28.3, 33.7, 53.0, 60.9, 66.0, 79.6, 98.3, 125.9, 128.6, 129.5, 130.0, 132.9, 138.8, 154.8, 169.4. IR ($CHCl_3$): 1166, 1456, 1637, 1712, 2851, 2921 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{22}H_{33}N_2O_6$ $[M + H]^+$): 421.2339; found: 421.2348.

(15) **General Procedure for the Addition of Grignard Reagent, R^1MgBr to the Weinreb Amides 9 and 14**

To a stirred solution of **9** or **14** (0.7 mmol) in anhyd THF (3 mL), the appropriate solution of alkyl or arylmagnesium bromide (4.2 mmol, 6 equiv) in anhyd THF (5 mL) was added under inert atmosphere at –10 °C and the mixture was stirred for 3 h between –10 °C and 0 °C. Subsequent hydrolysis was achieved by cautious addition of sat. NH_4Cl solution. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4, and concentrated to furnish the crude product, which was purified by silica gel column chromatography using hexane–EtOAc (85:15) to afford ketones **10a–e** and **15**, respectively. The spectral and analytical details for selected compounds are given below.

(*E*)-*tert*-Butyl [5-(4-Heptanoylstyryl)-2,2-dimethyl-1,3-dioxan-5-yl]carbamate (10b)

Yield 65%; R_f = 0.4 (hexane–EtOAc, 7:3); colorless solid, mp 86–89 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, 3 H, *J* = 7.2 Hz), 1.29–1.35 (m, 6 H), 1.44 (s, 9 H), 1.48 (s, 3 H), 1.49 (s, 3 H), 1.68–1.74 (m, 2 H), 2.94 (t, 2 H, *J* = 7.6 Hz), 3.91–4.01 (m, 4 H), 5.27 (br s, 1 H), 6.35 (d, 1 H, *J* = 16.4 Hz), 6.58 (d, 1 H, *J* = 16.4 Hz), 7.43 (d, 2 H, *J* = 8.0 Hz), 7.90 (d, 2 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 19.4, 22.5, 24.3, 27.7, 28.4, 29.0, 31.9, 38.6, 53.1, 66.1, 79.8, 98.4, 126.5, 128.5, 129.5, 131.0, 136.1, 140.9, 154.8, 200.0. IR ($CHCl_3$): 1167, 1466, 1601, 1682, 1716, 2853, 2923 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{26}H_{40}NO_5$ $[M + H]^+$: 446.2906; found: 446.2899.

(*E*)-*tert*-Butyl [2,2-Dimethyl-5-(4-octanoylstyryl)-1,3-dioxan-5-yl]carbamate (10d)

Yield 75%; R_f = 0.4 (hexane–EtOAc, 7:3); colorless solid, mp 83–86 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, *J* = 7.2 Hz), 1.28–1.38 (m, 8 H), 1.44 (s, 9 H), 1.47 (s, 3 H), 1.49 (s, 3 H), 1.70–1.74 (m, 2 H), 2.93 (t, 2 H, *J* = 7.2 Hz), 3.91–4.00 (m, 4 H), 5.25 (br s, 1 H), 6.35 (d, 1 H, *J* = 16.4 Hz), 6.58 (d, 1 H, *J* = 16.4 Hz), 7.43 (d, 2 H, *J* = 8.4 Hz), 7.90 (d, 2 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 19.5, 22.6, 24.5, 27.6, 28.4, 29.0, 29.3, 32.8, 38.6, 53.1, 66.1, 79.8, 98.4, 126.5, 128.4, 129.5, 131.0, 136.1, 140.9, 154.8, 199.9. IR ($CHCl_3$): 1168, 1456, 1603, 1685, 1719, 2853, 2923 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{27}H_{42}NO_5$ $[M + H]^+$: 460.3063; found: 460.3076.

(*E*)-*tert*-Butyl [5-(4-Benzoylstyryl)-2,2-dimethyl-1,3-dioxan-5-yl]carbamate (10e)

Yield 72%; R_f = 0.4 (hexane–EtOAc, 7:3); colorless solid, mp 109–112 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 1.48 (s, 3 H), 1.50 (s, 3 H), 3.92–4.01 (m, 4 H), 5.24 (br s, 1 H), 6.37 (d, 1 H, *J* = 16.4 Hz), 6.61 (d, 1 H, *J* = 16.4 Hz), 7.45–7.50 (m, 4 H), 7.57–7.59 (m, 1 H), 7.76–7.79 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 27.7, 28.4, 53.1, 66.1, 79.8, 98.4, 126.2, 128.2, 129.5, 129.9, 130.0, 132.3, 136.5, 137.7, 140.6, 154.8, 196.1. IR ($CHCl_3$): 1165, 1494, 1601, 1655, 1711, 2927, 2976 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{26}H_{32}NO_5$ $[M + H]^+$: 438.2280; found: 438.2281.

(16) (a) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (b) Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609. (c) See also ref. 4c and references cited therein.

(17) *Reagents and conditions*: (a) PPh_3 (1.2 equiv), acetone, reflux, 6 h, 80%; (b) $P(OEt)_3$ (1.5 equiv), toluene, 110 °C, 8 h, 60%.

{4-[Methoxy(methyl)carbamoyl]benzyl}(triphenyl)phosphonium Bromide (12)

Yield 80%; R_f = 0.2 (MeOH–$CHCl_3$, 3:7); white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.32 (s, 3 H), 3.57 (s, 3 H), 5.06 (d, 2 H, J_{HP} = 15.2 Hz), 7.12 (d, 2 H, *J* = 8.0 Hz), 7.49 (d, 2 H, *J* = 8.0 Hz), 7.69–7.76 (m, 12 H), 7.90–7.94 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.3, 30.8, 61.7, 118.5, 119.4, 129.6, 131.5, 131.8, 131.9, 132.0, 135.3, 135.5, 135.7, 136.6, 170.7. IR ($CHCl_3$): 1165, 1368, 1645, 3026 cm^{-1}.

Diethyl {4-[Methoxy(methyl)carbamoyl]benzyl}phosphonate (13)

Yield 60%; R_f = 0.1 (hexane–EtOAc, 3:7), colorless liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, 6 H, *J* = 6.8 Hz), 3.18 (d, 2 H, J_{HP} = 22.0 Hz), 3.35 (s, 3 H), 3.55 (s, 3 H), 4.00–4.06 (m, 4 H), 7.34 (dd, 2 H, *J* = 2.4, 8.0 Hz), 7.65 (d, 2 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3, 33.6 (d, J_{CP} = 140 Hz), 33.7, 60.9, 62.2, 128.5, 129.4, 132.5, 134.5, 169.5. IR ($CHCl_3$): 1019, 1220, 1380, 1633, 2981

cm^{-1}. HRMS (EI): *m/z* calcd for $C_{14}H_{23}NO_5P$ $[M + H]^+$: 316.1314; found: 316.1317.

(18) ***tert*-Butyl (5-{4-[Methoxy(methyl)carbamoyl]styryl}2,2-dimethyl-1,3-dioxan-5-yl)carbamate (9 + *Z*-isomer)**
Yield 70% (*Z*:*E* = 3:1); R_f = 0.35 (hexane–EtOAc, 6:4); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (*Z*-isomer) = 1.32 (s, 3 H), 1.38 (s, 9 H), 1.45 (s, 3 H), 3.37 (s, 3 H), 3.56 (s, 3 H), 3.77 (d, 2 H, *J* = 11.6 Hz), 3.88–3.94 (m, 2 H), 5.20 (br s, 1 H), 5.65 (d, 1 H, *J* = 12.8 Hz), 6.68 (d, 1 H, *J* = 12.8 Hz), 7.30 (d, 2 H, *J* = 8.0 Hz), 7.64 (d, 2 H, *J* = 8.0 Hz); δ (*E*-isomer, nonoverlapped signals) = 3.35 (s, 3 H), 3.53 (s, 3 H), 3.88–3.94 (m, 4 H), 5.27 (br s, 1 H), 6.23 (d, 1 H, *J* = 16.4 Hz), 6.48 (d, 1 H, *J* = 16.4 Hz), 7.39 (d, 2 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*Z*-isomer) = 18.8, 19.4, 20.9, 27.6, 28.3, 33.7, 52.5, 60.9, 65.8, 79.4, 98.1, 125.9, 128.6, 129.5, 130.0, 132.9, 140.1, 154.4, 169.4; δ (*E*-isomer, nonoverlapped signals) = 53.0, 66.0, 98.3, 127.9, 131.5, 132.6, 138.8. IR ($CHCl_3$): 1166, 1456, 1637, 1712, 2851, 2921 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{22}H_{33}N_2O_6$ $[M + H]^+$: 421.2339; found: 421.2348.

(19) ***tert*-Butyl (5-{4-[Methoxy(methyl)carbamoyl]phenethyl}-2,2-dimethyl-1,3-diox-an-5-yl)carbamate (14)**
Yield 95%; R_f = 0.35 (hexane–EtOAc, 6:4); colorless solid, mp 89–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 3 H), 1.44 (s, 3 H), 1.48 (s, 9 H), 1.98–2.02 (m, 2 H), 2.58–2.62 (m, 2 H), 3.35 (s, 3 H), 3.55 (s, 3 H), 3.69 (d, 2 H, *J* = 12.0 Hz), 3.90 (d, 2 H, *J* = 12.0 Hz), 5.01 (br s, 1 H), 7.21 (d, 2 H, *J* = 8.0 Hz), 7.60 (d, 2 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9, 27.4, 28.3, 28.6, 32.3, 32.8, 50.6, 59.9, 65.2, 78.4, 97.4 126.1, 126.9, 127.5, 130.6, 143.9, 153.9, 168.8. IR ($CHCl_3$): 1164, 1453, 1638, 1710, 2934, 2976 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{22}H_{35}N_2O_6$ $[M + H]^+$: 423.2495; found: 423.2486.

(20) ***tert*-Butyl [2,2-Dimethyl-5-(4-octanoylphenethyl)-1,3-dioxan-5-yl]carbamate (15)**
Yield 70%; R_f = 0.4 (hexane–EtOAc, 7:3); colorless solid, mp 60–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, *J* = 6.8 Hz), 1.25–1.35 (m, 8 H), 1.42 (s, 3 H), 1.44 (s, 3 H), 1.47 (s, 9 H), 1.70–1.74 (m, 2 H), 1.99–2.11 (m, 2 H), 2.60–2.64 (m, 2 H), 2.92 (t, 2 H, *J* = 7.2 Hz), 3.69 (d, 2 H, *J* = 12.0 Hz), 3.89 (d, 2 H, *J* = 12.0 Hz), 4.95 (br s, 1 H), 7.26 (d, 2 H, *J* = 8.0 Hz), 7.87 (d, 2 H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.2, 19.0, 21.7, 23.7, 26.3, 27.6, 28.2, 28.5, 28.8, 30.8, 32.4, 37.7, 50.9, 65.5, 78.8, 97.6, 127.5, 127.7, 134.4, 146.7, 154.1, 199.3. IR ($CHCl_3$): 1198, 1498, 1606, 1682, 1715, 2856, 2926 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{27}H_{44}NO_5$ $[M + H]^+$: 462.3219; found: 462.3229.