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Tetrahedron Letters 46 (2005) 6691–6695
Tetrahedron Letters

A simple spiroepoxide as methionine aminopeptidase-2 inhibitor: synthetic problems and solutions

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Received 6 July 2005; revised 25 July 2005; accepted 26 July 2005
Available online 10 August 2005

Abstract—The preparation of a simple 1-oxa-spiro[2.4]heptane derivative is described. Observations made in the course of the synthesis show again that apparently minor structural modifications of the dienic substrate exert a strong influence on the ring-closing metathesis outcome and that the efficient construction of even simple but highly substituted systems by RCM may constitute a synthetic challenge.

In a previous work on angiogenesis inhibitors based on the fumagillin structure (**1**),[1] we showed that the parent molecule could be simplified without loss of biological activity, as measured by MetAP-2 inhibition. In these studies, however, the overall structure of fumagillin was still conserved (**2**) (Fig. 1).

In an attempt to bypass lengthy structure–activity relationship (SAR) studies towards simple molecules endowed with MetAP-2 inhibition properties, we decided to perform drastic changes on the parent molecule skeleton. From the literature data and our earlier work, we knew that certain features such as an *exo* epoxide

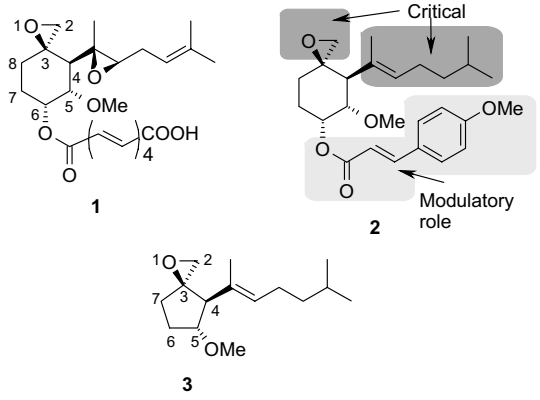
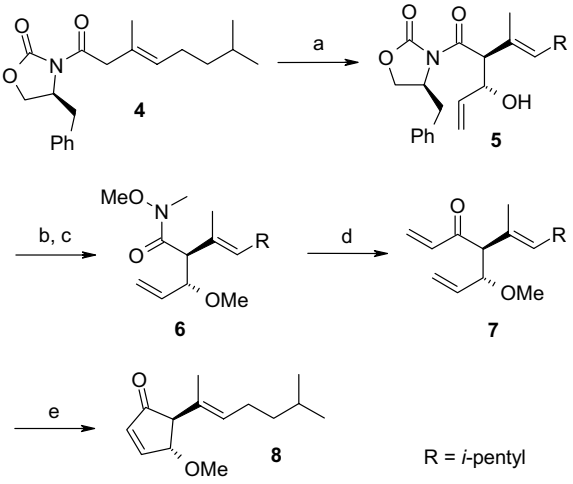


Figure 1.



Scheme 1. Reagents and conditions: (a) (i) n-Bu_2BOTf (1 M in CH_2Cl_2, 1.2 equiv), Et_3N (1.3 equiv), CH_2Cl_2, −78 °C (30 min) then 0 °C (20 min); (ii) acrolein (5 equiv), −78 °C (1 h) → 0 °C (1 h), then MeOH, pH 7 buffer and 30% H_2O_2, 27%; (b) Me(MeO)NH·HCl, $AlMe_3$ (2 M in toluene, 3.5 equiv), THF, 0 °C, 14 h; (c) MeI (excess), Ag_2O, mol. sieves 4 Å, Et_2O, 40 °C, 8 h, 50%; (d) CH_2=CH–MgBr (1 M in THF, 5 equiv), **6**, THF, 0 → 20 °C, 12 h, THF, then NH_4Cl, 50%; (e) **[Ru]-2** (10 mol %), toluene, 70 °C, 4 h, 60%.

Keywords: RCM; MetAP-2; Inhibition; Fumagillin.
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doi:10.1016/j.tetlet.2005.07.136

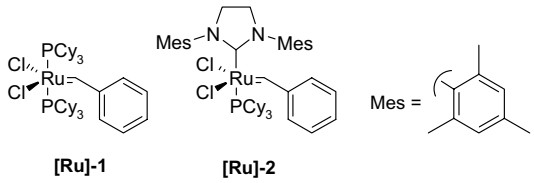


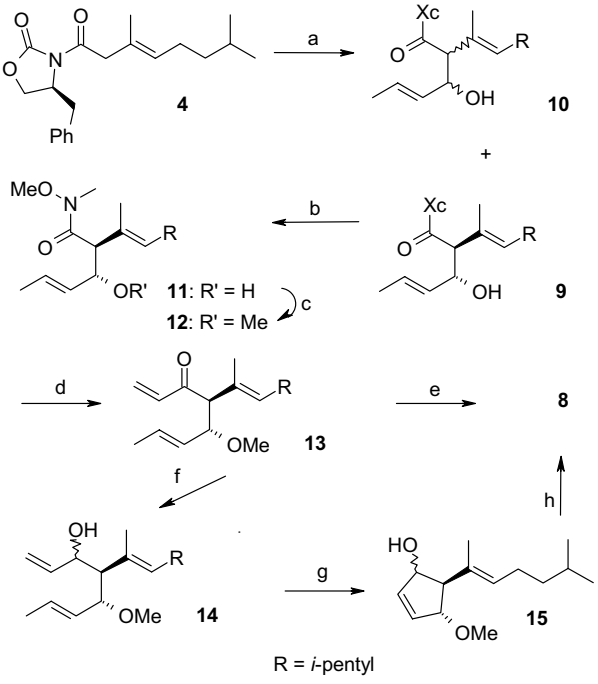
Figure 2.

and a 1,5-dimethyl-hex-1-enyl side chain were required for activity[2] and it is known that modification of the substituent at C-6 modulates, but does not suppress activity.[3] Even replacement of the C-6 substituent by H seems to be compatible with significant biological activity.[4] The above considerations led us to select the simple spiroepoxide **3** (Fig. 1), which in our view, represented the minimal structure required for biological activity, as our target molecule.

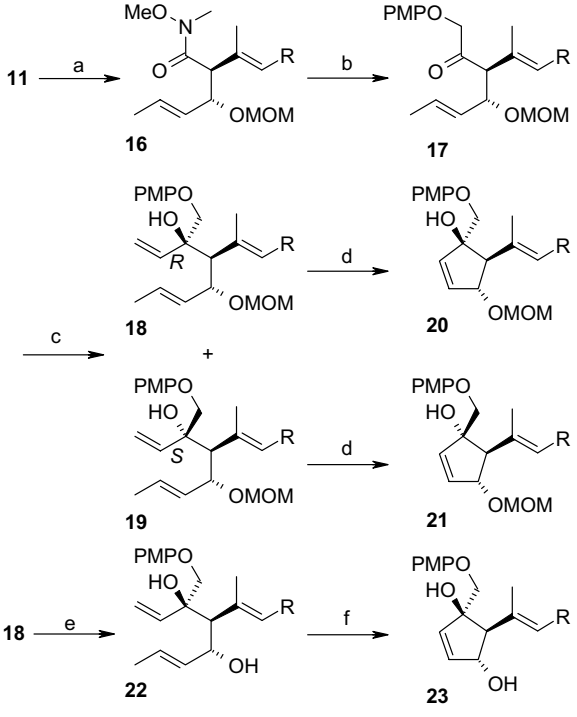
Considering the structural simplicity of **3**, we anticipated its synthesis to present no serious problem. Our initial approach, shown in Scheme 1, takes advantage of a reliable Evans aldolization/RCM sequence that we had used successfully in a previous work. The required Evans (*S*)-oxazolidinone **4** was prepared as previously described for the (*R*)-enantiomer and coupled with acrolein. Standard conversion to the α,β-unsaturated ketone **7** followed by RCM using **[Ru]-2** (Fig. 2) as catalyst afforded cyclopentenone **8**.

Unfortunately, while the RCM worked reasonably well, the Evans aldolization proceeded only in poor yield to afford a single aldol (27%, optimized), to which the expected structure shown in Scheme 1 was attributed. This contrasts with the fair-to-good yields reported for the few similar condensations that have been published.[5]

Following this disappointing result, we modified our approach as shown in Scheme 2. The Evans aldolization was now performed using crotonaldehyde instead of acrolein to afford in excellent overall yield a 75:25 mixture of two aldols, which could be separated by chromatography. The absolute configurations in the major aldol **9** are again assumed to be those predicted by the rules applying to the Evans reaction using boron enolates. While the overall sequence leading to **13** was satisfactory, the RCM reaction (catalyst: **[Ru]-2**) was very sluggish, affording cyclopentenone **8** in low (30%) yield. The latter problem could be solved by a slight modification of our synthetic scheme: Luche reduction of ketone **13** afforded the corresponding allylic alcohol **14**, which as expected, smoothly ring-cyclized to cyclopentenol **15**.[6] Oxidation using Dess–Martin periodinane led to



Scheme 2. Reagents and conditions: (a) (i) *n*-Bu_2BOTf (1 M in CH_2Cl_2, 1.1 equiv), Et_3N (1.3 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) crotonaldehyde (1.5 equiv), −78 °C (1 h) → −20 °C (20 h), then MeOH, pH 7 buffer and 30% H_2O_2, 62% (**9**) and 22% (**10**); (b) Me(MeO)NH·HCl (3.5 equiv), $AlMe_3$ (2 M in toluene, 3.5 equiv), THF, 0 °C, 14 h, 80%; (c) MeI (excess), Ag_2O, mol. sieves 4 Å, Et_2O, 40 °C, 8 h, 90%; (d) CH_2=CH–MgBr (1 M in THF, 5 equiv), **12**, THF, 0 → 20 °C, 12 h, THF, then NH_4Cl, 52%; (e) **[Ru]-2** (15 mol %), toluene, 70 °C, 4 h, 30%; (f) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 30 min; (g) **[Ru]-2** (15 mol %), CH_2Cl_2, 40 °C, 1 h (quantitative); (h) Dess–Martin periodinane, CH_2Cl_2, 20 °C, 1 h, 55% (three steps).



Scheme 3. Reagents and conditions: (a) MOM-Cl (2 equiv), *i*Pr_2NEt (4 equiv), CH_2Cl_2, 20 °C, 16 h, 81%; (b) (i) tributyl-(4-methoxyphenoxymethyl)-stannane (2.8 equiv), BuLi (2.75 equiv), THF, −78 °C, 30 min; (ii) **16**, −78 °C, 30 min, 64%; (c) CH_2=CH–MgBr (1 M in THF, 3 equiv), THF, −78 °C, 2 h, 51%; (d) **[Ru]-2** (15 mol %), CH_2Cl_2, 40 °C, 30 h, 42% (**20**), 48% (**21**); (e) $BF_3{\cdot}Me_2S$ (6 equiv), CH_2Cl_2, Me_2S, −78 °C, 3 h, 10–45%; (f) **[Ru]-2** (5 mol %), CH_2Cl_2, 40 °C, 1 h, 80%.

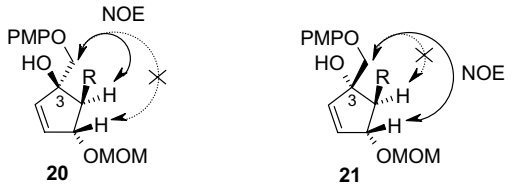


Figure 3.

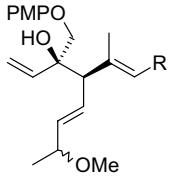
cyclopentenone **8**. The overall yield from **13** to **8** via **14** was a satisfactory, unoptimized 55%, the best result being the quantitative RCM step.

Unfortunately, it rapidly became clear that cyclopentenone **8** was very unstable and readily eliminated methanol upon basic treatment, jeopardizing the next steps of the synthesis (Corey or Mattheson epoxidation of the ketone). Thus, although we had been successful in improving the sequence **4**→**8**, it appeared that we had reached a dead-end regarding the preparation of our ultimate target molecule **3** and that we needed to more drastically rethink our original plans.

We then turned to the alternative approach shown in Scheme 3 that capitalizes on our previous positive results: Evans reaction using crotonaldehyde and reactive RCM substrate. A protected diol is introduced before cyclization and will be converted to an epoxide towards the end of the synthesis, thus avoiding the problematic cyclopentenone step. With the idea of introducing various substituents at position 5, we decided to replace the 5-methoxy group (see **3**, Fig. 1 for numbering) used until now by the readily cleavable MOM protecting group. Thus the Weinreb amide **11** was treated with MOMCl to afford the corresponding ether **16** in good yield, which was converted to ketone **17** in 64% yield by treatment with 4-methoxy-phenoxymethyllithium.[7] The reaction of ketone **17** with vinylmagnesium bromide gave a 7:3 mixture of two isomers (**18** and **19**), which could be separated by chromatography. Both isomers underwent slow ring closure, using **[Ru]-2** as catalyst to furnish the corresponding cyclopentenols in modest (42% and 48%, respectively), yield.

The absolute configuration at C-3 in **20** and **21** was determined from the observed NOEs (Fig. 3).

In an attempt to improve the yields at the RCM step, the MOM protecting group was removed (Scheme 3). This seemingly simple operation proved to be quite troublesome. Under classical conditions (cat. *p*-toluenesulfonic acid in methanol), only a transposed allylether **24** was obtained in 80% yield from **18**.



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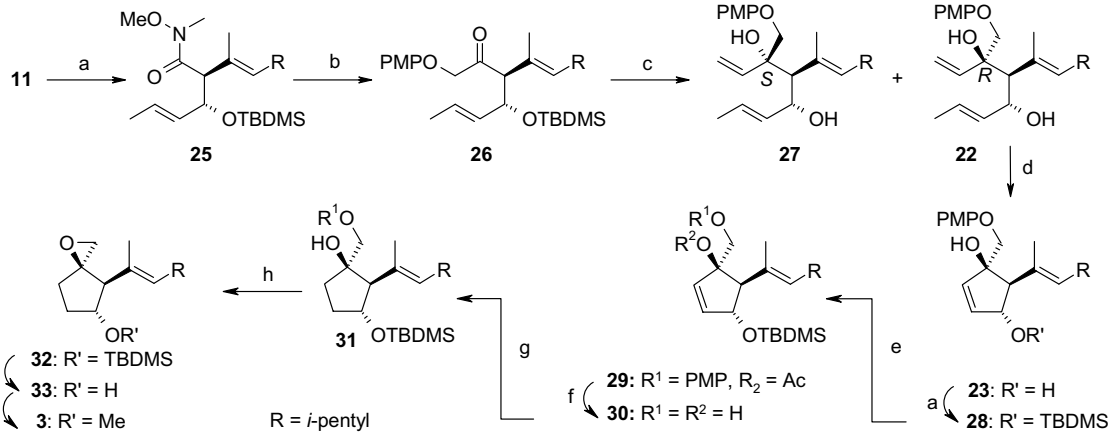
Using the conditions developed by Gennari and coworkers[8] for cleaving sensitive MOM ethers, the desired allylic alcohol **22** could be obtained but the yield remained modest and variable (10–45%). As expected, RCM now proceeded smoothly, affording cyclopentenol **23** in 80% yield (non-optimized).

Taking into account the observations made during this work, a final, optimized synthetic route that eventually led to our target molecule **3** was devised (Scheme 4).[9]

Table 1. MetAP-2 inhibition by fumagillin and analogues **2** and **3**

Compound	IC_{50} (nM)
Fumagillin	10
2	15
3	3000



Scheme 4. (a) TBDMSOTf (2 equiv), 2,6-lutidine (2 equiv), CH_2Cl_2, −78 °C, 1 h, 98% (**25**) and 96% (**28**); (b) *p*-methoxyphenoxymethyl(tributyl)tin (2.9 equiv), BuLi (2.8 equiv), THF, −78 °C, 30 min; (c) CH_2=CH–MgBr (1 M in THF, 3 equiv), THF, −78 °C, 2 h, 24% (**27**) and 33% (**22**) (two steps); (d) **[Ru]-2** (5 mol %), CH_2Cl_2, 40 °C, 1 h, 95%; (e) Ac_2O (2 equiv), DMAP (cat.), pyridine, 40 °C, 24 h, 54%; (f) (i) CAN (2 equiv), CH_3CN/pH 7 phosphate buffer, 0 °C, 30 min; (ii) K_2CO_3, MeOH, 1 h, 0 °C, 66%; (g) $Rh(PPh_3)_3Cl$ (10 mol %), H_2, toluene, 14 h, 80 °C; (h) (i) MsCl (1.2 equiv), Et_3N (3 equiv), CH_2Cl_2, 0 °C, 1 h; (ii) NaOH (0.25 M in MeOH, 5 equiv), 20 °C, 30 min; (i) NBu_4F (1 M in THF, 5 equiv), mol. Sieves 4 Å, THF, 13% (from **30**); (j) MeI (10 equiv), Ag_2O (5 equiv), mol. sieves 4 Å, diethyl ether, reflux, 2 h, 50%.

Table 2. RCM to form cyclopentenols or cyclopentenones

Substrate	Conditions	Time (h)	Yield (%)
13	**[Ru]-2** (15 mol %), toluene, 70 °C	4	30
	[Ru]-1 (15 mol %), $Ti(OiPr)_4$ (30%), toluene, 70 °C	4	<5
7	**[Ru]-2** (10 mol %), toluene, 70 °C	4	60
14	**[Ru]-2** (7 mol %), CH_2Cl_2, 40 °C	1	Quantitative
18	**[Ru]-2** (15 mol %), CH_2Cl_2, 40 °C	30	50% conversion
22	**[Ru]-2** (5 mol %), CH_2Cl_2, 40 °C	1	95

Protection of the free hydroxyl by a *tert*-butyldimethylsilyl group in Weinreb amide **11** was followed by sequential addition of *p*-methoxyphenoxymethyl lithium and vinyl magnesium bromide. The crude mixture of carbinols was desilylated to afford a nearly 1:1 mixture of the desired *R*-diol **22** and its 3-*epi*-isomer **27** in good yield. The two compounds were separated and **22** was submitted to RCM conditions to afford **23**. The secondary and tertiary alcohols in **23** were protected as the corresponding *tert*-butyldimethylsilyl ether and acetate, respectively, and the PMP was removed by CAN-induced oxidative cleavage.[10] The final steps include deacetylation, selective reduction of the allylic double bond[11] and mesylation/epoxide formation, then removal of the TBDMS group and methylation of the secondary alcohol to afford **3**. The compound was evaluated in our MetAP-2 assay.[1b] Despite its considerably simplified structure as compared to fumagilline or fumagillol, the compound exhibited moderate MetAP-2 inhibitory activity (300 times less than fumagillin) (Table 1).[12]

The results of our metathesis experiments (Table 2) show again the crucial role of substituents on (or close to) the dienic system and illustrate how these can be optimized for maximal efficacy. Initially, we worked with electron-poor systems in which one of the olefins carried an α-keto group. In this case acceptable yields were only obtained with monosubstituted olefins (compare **7** and **13**). Replacement of the keto group by a secondary alcohol (**14**) restored reactivity and led to quantitative yields of cyclized product. This reactivity was again strongly decreased for **18**, featuring a tertiary allylic alcohol, probably reflecting the difficulty for the catalyst to reach the now hindered coordination site. Simply providing a new site of coordination for the catalyst again restored the reactivity towards metathesis conditions (**22**). This demonstrates once again how the nature of substituents can drastically alter the reactivity of dienic systems in RCM and shows that simple manipulation of protective groups may provide an answer to the problems posed by difficult metatheses.[13]

In conclusion, the synthesis of a simple, chiral spiro-epoxide, which initially appeared to be a simple task, required careful adjustment of the synthetic intermediates at nearly all steps. Noteworthy is, in our case, the strong difference between acrolein and crotonaldehyde as electrophilic partner in the Evans reaction and the very strong influence of the 1,6-diene substitution pattern on the RCM outcome.

Acknowledgements

We thank Drs. Didier Le Nouen and Stéphane Bourg for help with NMR recording and interpretation. We thank the CNRS and Galderma R&D for a fellowship to V.R. Financial support for this project by Galderma R&D is gratefully acknowledged.

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9. Analytical data for selected compounds: **9**. $[\alpha]_D^{20}$ +28 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): 7.18–7.27 (m, 5H, Ar*H*), 5.77 (m, 1H, C*H*=CH–CHOH), 5.60 (t, $J = 7.0$, 1H, C=C*H*–CH_2), 5.50 (dd, $J = 15.4$, 5.8, 1H, CH=C*H*–CHOH), 4.69 (m, 1H, C*H*–CH_2–Phe), 4.51 (m, 2H, C*H*–OH and (C=O)–C*H*), 4.13 (m, 2H, N–CO_2CH_2), 3.22 (dd, $J = 13.3$, 3.5, 1H, C*H*H–Phe), 2.65 (dd, $J = 13.3$, 9.8, 1H, C*H*H–Phe), 2.20 (d, $J = 2.3$, 1H, CH–O*H*), 2.10 (q, $J = 7.0$, 2H, CH_2–CH=C), 1.80 (s, 3H, CH_3–C=CH), 1.68 (br d, $J = 6.5$, 3H, *Me*–CH=CH), 1.56 (m, 1H, C*H*$(Me)_2$), 1.27 (m, 2H, CH_2–CH$(Me)_2$), 0.88 (d, $J = 6.5$, 6H $(CH_3)_2$CH). ^{13}C NMR (100 MHz, $CDCl_3$): 172.1 ((*C*O)CH), 152.8 (O–(*C*=O)–N), 135.2 (HC=*C*(Me)), 133.7 ((Me)C=*C*H), 130.9 (CH=*C*H–CH(OH), 129.4

(Ar), 128.9 (Ar), 128.8 (*C*H=CH–CH(OH)), 127.6 (Ar), 127.4 (Ar), 71.6 (*C*H(OH)), 65.9 ((C=O)–O–*C*H_2), 57.6 ((C=O)–*C*H), 54.9 (*C*H–CH_2–Phe), 38.6 (*C*H_2–CH(CH_3)), 37.7 (*C*H_2–Phe), 27.8 (*C*H–(CH_3)$_2$), 26.2 (*C*H_2–CH=C), 22.6 ((CH_3)$_2$), 17.8 (*C*H_3–CH=CH), 15.1 (*C*H_3–C=CH). Anal. Calcd for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51. Found: C, 71.82; H, 8.64; N, 3.37.

Compound **11**. $[\alpha]_D^{20}$ −124 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 5.75 (m, 1H, C*H*=CH–CHOH), 5.48 (ddd, *J* = 13.6, 6.6, 1.8, 1H, CH=C*H*–CHOH), 5.40 (t, *J* = 6.4, 1H, C=C*H*–CH_2), 4.47 (t, *J* = 6.6, 1H, C*H*–OH), 3.64 (s, 3H, *Me*–O–N), 3.46 (m, 1H, (C=O)–C*H*), 3.16 (s, 3H, *Me*–N), 2.98 (br s, 1H, CH–O*H*), 2.09 (m, 2H, CH_2–CH=C), 1.74 (s, 3H, CH_3–C=CH), 1.68 (d, *J* = 6.3, 3H, *Me*–CH=CH), 1.55 (m, 1H, C*H*(CH_3)$_2$), 1.24 (m, 2H, CH_2–CH(CH_3)$_2$), 0.88 (d, *J* = 6.5, 6H (CH_3)$_2$CH). ^{13}C NMR (100 MHz, $CDCl_3$): 132.2 (H*C*=C(Me)), 131.9 ((Me)*C*=CH), 131.0 (CH=*C*H–H(OH), 127.8 (*C*H=CH–CH(OH)), 71.8 (*C*H(OH)), 61.3 (Me–O–N), 56.2 ((C=O)–*C*H), 38.7 (*C*H_2–CH(CH_3)), 31.9 (Me–N), 27.7 (*C*H–(CH_3)$_2$), 26.0 (*C*H_2–CH=C), 22.5 ((CH_3)$_2$), 17.8 (*C*H_3–CH=CH), 15.2 (*C*H_3–C=CH). Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31; N, 4.94. Found: C, 67.98; H, 10.27; N, 4.91.

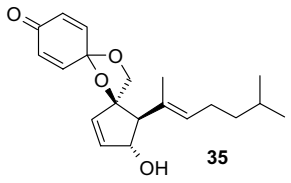
Compound **22**. $[\alpha]_D^{20}$ −22 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 6.78 (m, 4H, Ar–*H*), 6.13 (dd, *J* = 17.2, 10.4, 1H, CH_2=C*H*), 5.63 (dq, *J* = 15.0, 6.0, 1H, Me–C*H*=CH), 5.56 (dd, *J* = 17.2, 1.2, 1H, CH*H*=CH), 5.45 (ddd, *J* = 15.0, 6.8, 1.2, 1H, CH=C*H*–CH(OH)), 5.32 (dd, *J* = 10.4, 1.2, 1H, CH*H*=CH), 5.32 (m, 1H, (Me)C=C*H*), 4.64 (dd, *J* = 6.8, 2.8, 1H, C*H*–OH), 3.82 and 3.70 (2 d, AB, *J* = 8.8, 2H, CH_2-OAr), 3.75 (s, 3H, O*Me*), 2.29 (d, *J* = 2.8, 1H, C*H*–C(Me)=C), 2.00 (q, *J* = 7.5, 2H, C=CH–CH_2), 1.67 (s, 3H (*Me*)C=C), 1.66 (d, *J* = 6.0, 3H, CH_3–CH=CH), 1.48 (m, 1H, C*H*(CH_3)$_2$), 1.12 (q, *J* = 7.5, 2H, CH_2–CH(CH_3)$_2$), 0.82 (d, *J* = 6.6, 6H (CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): 153.9, 152.9, 142.1, 132.6, 132.4, 131.1, 126.7, 115.5, 114.6, 114.5, 78.3, 77.2, 73.7, 56.3, 55.7, 38.7, 27.5, 25.7, 22.5, 22.4, 17.6. Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.08; H, 9.63.

Compound **30**. $[\alpha]_D^{20}$ −87 (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 5.94 (dd, *J* = 5.6, 2.0, 1H, CH=C*H*–CHOTBS), 5.87 (d, *J* = 5.6, 1H, C*H*=CH–CHOTBS), 5.32 (t, *J* = 6.8, 1H, C(Me)=C*H*), 4.87 (br s, 1H, C*H*OTBS), 3.58 (m, 2H, CH_2–OH), 2.49 (d, *J* = 3.6, 1H, C*H*–C(Me)=C), 2.31 (br s, 1H, O*H*), 2.16 (br s, 1H, O*H*), 2.06 (m, 2H, C=CH–CH_2), 1.66 (s, 3H, (*Me*)C=C), 1.55 (m, 1H, C*H*(CH_3)$_2$), 1.25 (q, *J* = 7.5, 2H, CH_2–CH(CH_3)$_2$), 0.89 (d, *J* = 6.8, 6H, (CH_3)$_2$), 0.87 (s, 9H, ^{t}Bu), 0.04 (s, 6H, (*Me*)$_2$Si). ^{13}C NMR (100 MHz, $CDCl_3$): 137.6, 135.7, 132.7, 130.2, 84.2, 80.4, 69.3, 62.8, 38.8, 27.7, 25.9, 25.8, 22.6, 22.5, 18.1, 17.5, −4.7. HRMS *m*/*z* found 323.2408, calcd for $C_{19}H_{35}O_2Si$ *m*/*z* 323.2406.

Compound **33**. $[\alpha]_D^{20}$ −36 (*c* 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 5.18 (t, *J* = 6.6, 1H, C=C*H*), 4.37 (dt, *J* = 8.8, 6.4, 1H, C*H*OH), 2.70 and 2.66 (2 d, AB, *J* = 5.2, 2H, CH_2-époxyde), 2.49 (d, *J* = 8.8, 1H, C*H*–C(Me)=C), 2.25–2.20 (m, 1H, C*H*H–CHOH), 2.20–2.10 (m, 1H, C*H*H–CH_2–CHOH), 2.00 (m, 2H, C=CH–CH_2), 1.80 (m, 1H, CH*H*–CH_2–CHOH), 1.66 (s, 3H, (*Me*)C=C), 1.56–1.48 (m, 3H, CH*H*–CHOH, C*H*(CH_3)$_2$ and O*H*), 1.22 (q, *J* = 7.4, 2H, CH_2–CH(CH_3)$_2$), 0.87 (d, *J* = 6.8, 6H, (CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): 131.4, 129.7, 74.1, 63.0, 60.4, 50.1, 38.9, 31.9, 29.7, 27.7, 25.9, 22.6, 22.5, 14.5. HRMS *m*/*z* found 224.1763, calcd for $C_{14}H_{24}O_2$ *m*/*z* 224.1776.

Compound **3**. $[\alpha]_D^{20}$ −27 (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 5.15 (t, *J* = 6.8, 1H, C=C*H*), 3.97 (m, 1H, C*H*OMe), 3.36 (s, 3H, O*Me*), 2.70 and 2.57 (2 d, *J* = 5.2, AB, 2H, CH_2(époxyde)), 2.61 (d, *J* = 8.0, 1H, C*H*–C(Me)=CH), 2.15 (m, 2H, CH_2), 2.01 (m, 2H, C(Me)=CH–CH_2), 1.80-1.50 (m, 3H, C*H*(CH_3)$_2$ and CH_2), 1.64 (s, 3H, Me), 1.20 (m, 2H, CH_2–CH(CH_3)$_2$), 0.87 (d, *J* = 6.8, 6H, CH(*Me*)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): 130.1, 127.4, 83.2, 61.4, 57.9, 57.0, 49.9, 38.8, 29.9, 29.3, 27.8, 25.9, 22.6, 22.5, 14.8. HRMS *m*/*z* 238 (M^+).

10. Failure to protect the tertiary alcohol before PMP removal led to formation of the stable quinone ketal **35**. A similar observation has been made previously: Leung, L. W.; Vilchèze, C.; Bittman, R. *Tetrahedron Lett.* **1998**, *39*, 2921–2924



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