Tetrahedron 69 (2013) 2052–2055

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Microwave-assisted Diels–Alder reactions between Danishefsky's diene and derivatives of ethyl α-(hydroxymethyl)acrylate. Synthetic approach toward a biotinylated anti-inflammatory monocyclic cyanoenone

Suqing Zheng [a], Allison Chowdhury [a], Iwao Ojima [a,b], Tadashi Honda [a,b,*]

[a] Institute of Chemical Biology and Drug Discovery, Stony Brook University, Stony Brook, NY 11794, United States
[b] Department of Chemistry, Stony Brook University, Stony Brook, NY 11794, United States

ARTICLE INFO

Article history:
Received 13 November 2012
Received in revised form 12 December 2012
Accepted 14 December 2012
Available online 9 January 2013

Keywords:
Microwave
Diels–Alder reaction
Danishefsky's diene
α-(Hydroxylmethyl)acrylate
Monocyclic cyanoenones

ABSTRACT

The microwave heating drastically accelerates Diels–Alder cycloadditions between Danishefsky's diene and derivatives of ethyl α-(hydroxymethyl)acrylate whose hydroxyl group is protected with various protective groups to give previously unknown adducts, which are necessary as intermediates for the synthesis of a biotin conjugate of a monocyclic cyanoenone with high anti-inflammatory activity. The reaction time is only 1 h and the average yield is approximately 80%. Compared to the traditional thermal conditions this method requires 1/48th to 1/14th of the time and the yields are 2–7 times more.

1. Introduction

Monocyclic cyanoenones, examined to date, display unique and interesting features with respect to both chemical reactivity as Michael acceptors and biological potency.[1,2] Among monocyclic cyanoenones, 3-ethynyl-3-methyl-6-oxocyclohexa-1,4-dienecarbonitrile (MCE-1, Fig. 1) functions as a very reactive Michael acceptor with thiol nucleophiles. Furthermore an important feature of MCE-1 is that its Michael addition is reversible (if the addition is irreversible, the bioavailability would be drastically decreased by scavenger nucleophiles, such as glutathione). Remarkably, in some biological assays related to inhibition of inflammation and carcinogenesis, MCE-1 is more potent than pentacyclic triterpenoids, CDDO and its methyl ester, bardoxolone methyl, which has shown a significant increase in estimated glomerular filtration rate (eGFR), compared with no change in the placebo group in a multi-center, double-blind, placebo-controlled Phase 2b clinical trial in type 2 diabetic patients with severe chronic kidney disease (Fig. 1)[3–6] and a tricycle, TBE-31, which is currently the most potent among semi-synthetic pentacyclic triterpenoids and synthetic tricycles (Fig. 1).[7,8]

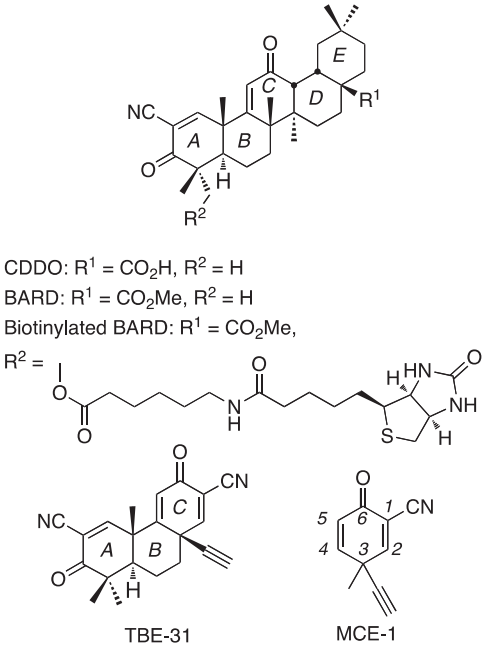
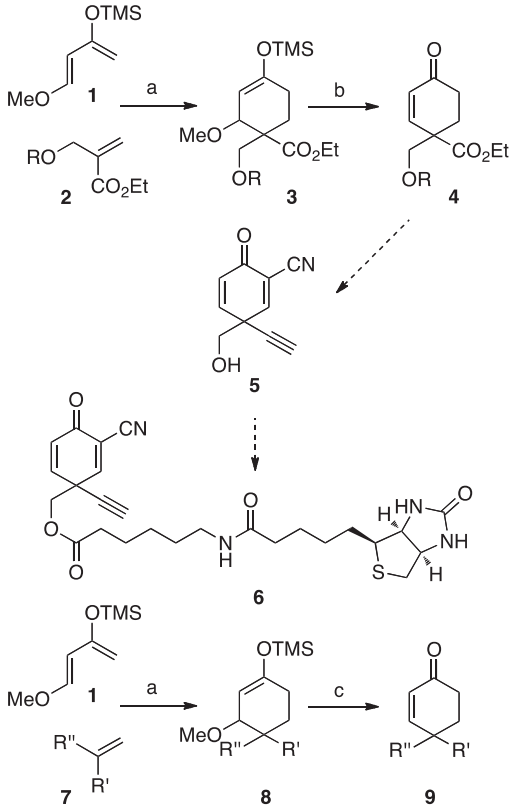


Fig. 1. Structures of CDDO, bardoxolone methyl (BARD), biotinylated bardoxolone methyl, TBE-31, and MCE-1.

* Corresponding author. Tel.: +1 631 632 7162; fax: +1 631 632 7942; e-mail address: tadashi.honda@stonybrook.edu (T. Honda).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.12.079

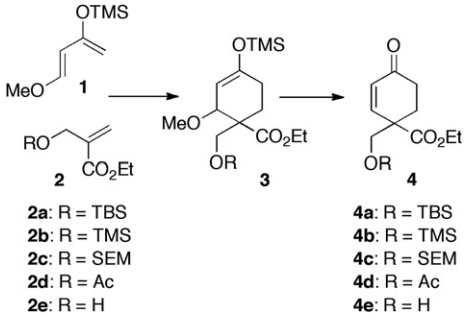
For the clarification of the mechanisms, identification of the protein targets is essential. Two protein targets of bardoxolone methyl were identified using its biotin conjugate, biotinylated bardoxolone methyl (Fig. 1).[9–11] Based on the structure of the biotin conjugate, we have designed a new biotin conjugate **6** (Scheme 1) for identifying the protein targets of MCE-1, which can be synthesized from a new compound **5**. For our projected synthesis, previously unknown compounds **4** are necessary as the intermediates. We have envisioned that Diels–Alder reactions between Danishefsky's diene **1** and derivatives of ethyl α-(hydroxymethyl)acrylate **2** whose hydroxyl group is protected with various protective groups, followed by deprotection, would give new adducts **4** via **3** (Scheme 1). However, the traditional thermal conditions of the Diels–Alder reaction gave desired adducts **4** only in very low yield (see Table 1), while the cycloadditions between methacrylic acid derivatives **7** [(R′=Me and R″=CO_2Me, CHO, CN) and (R′=CH(OTBS)Me and R″=CO_2Me)], whose structures are similar to those of **2**, and diene **1** under the same conditions gave the adducts **9** in good yields (86–100%).[2,12] Also, Lewis acid catalyzed conditions did not give the adducts probably due to the instability of diene **1** under the conditions.



Scheme 1. Reagents and conditions: (a) heat, solvents; (b) CSA or PPTS, THF at 60 °C; (c) CSA, Et_2O at rt.

In the past few years, microwave-assisted organic synthesis has been an increasingly popular theme in the scientific community. Diels–Alder reactions have been successful with the aid of microwave heating, as they require, in many cases, the use of high temperatures, long reaction times, and high pressures.[13–16] However, only a few reports about the microwave-assisted cycloadditions using Danishefsky's diene **1** have been published.[17] During the exploration of our projected synthesis of **6**, we found that microwave heating strongly accelerates our Diels–Alder cycloadditions to give adducts **3** in very good yield whilst the thermal and Lewis acid catalytic conditions do not. Thus, we have extensively investigated these reactions using several dienophiles **2a**–**e**. In each case, we have observed drastic differences between the traditional methods and the microwave conditions. Herein, we report the Diels–Alder cycloadditions between Danishefsky's diene **1** and derivatives of ethyl α-(hydroxymethyl)acrylate **2** under the microwave conditions.

Table 1
Diels–Alder reactions between Danishefsky's diene **2** and various dienophiles **1**



Entry	2	Solvent	Temp (°C)	Time (h)	4	Yield (%)
1	**2a**	Toluene[a]	130	48	**4a**	25[c]
2	**2a**	*o*-Dichlorobenzene[b]	180	20	**4a**	45[d]
3	**2a**	*o*-Dichlorobenzene	150 (MW)	1	**4a**	72[c]
4	**2a**	Neat	150 (MW)	1	**4a**	87[c]
5	**2b**	Toluene[a]	130	24	**4e**	29[e]
6	**2b**	*o*-Dichlorobenzene[b]	180	21	**4b**	14[d]
7	**2b**	*o*-Dichlorobenzene	150 (MW)	1	**4e**	80[c]
8	**2b**	Neat	150 (MW)	1	**4e**	77[e]
9	**2c**	Toluene[a]	130	24	**4e**	12[e]
10	**2c**	*o*-Dichlorobenzene	150 (MW)	1	**4c**	74[c]
11	**2c**	Neat	150 (MW)	1	**4c**	82[c]
12	**2d**	Toluene[a]	130	24	**4d**	36[c]
13	**2d**	*o*-Dichlorobenzene[b]	180	14	**4d**	25[d]
14	**2d**	*o*-Dichlorobenzene	150 (MW)	1	**4d**	85[c]
15	**2d**	Neat	150 (MW)	1	**4d**	76[c]
16	**2e**	*o*-Dichlorobenzene[b]	180	18	—	—
17	**2e**	*o*-Dichlorobenzene	150 (MW)	1	**4e**	29[c]
18	**2e**	*o*-Dichlorobenzene	180 (MW)	1	**4e**	76[c]
19	**2e**	Neat	150 (MW)	1	—	—

MW: microwave heating; —: no adduct was produced.
[a] In a sealed tube.
[b] Under reflux.
[c] Adduct **4** was obtained from **3** with PPTS in THF at 60 °C for 2 h.
[d] Adduct **4** was directly obtained from the cycloaddition without CSA or PPTS.
[e] Adduct **4** was obtained from **3** with CSA in THF at 60 °C for 2 h.

2. Results and discussion

Known dienophiles **2a**,[18] **2b**,[19] and **2d**[20] were synthesized from the known ethyl α-(hydroxylmethyl)acrylate (**2e**),[21] which was obtained from ethyl acrylate and formaldehyde. New dienophile **2c** was synthesized in 97% yield from **2e** with SEMCl in the presence of ethyldiisopropylamine in CH_2Cl_2.

Initially we tried to prepare a new adduct **4a** whose hydroxyl group is protected with a TBS group because we considered that this adduct is the most appropriate intermediate for the synthesis of **5** among various protected adducts **4a**–**d**. However, adduct **4a** was obtained in only 25% yield by the cycloaddition between **1** and **2a** in toluene in a sealed tube (at 130 °C) for 48 h, followed by removal of the protective groups with PPTS in THF (at 60 °C) for 2 h (entry 1 in Table 1). Even higher temperature conditions (in *o*-dichlorobenzene under reflux at 180 °C for 20 h) gave **4a** in moderate yield (45%, entry 2). We speculated that this cycloaddition does not give **4a** in good yield because the TBS group is bulky. Secondly, we used dienophile **2b**

with a TMS group, which is less bulky than a TBS group, but the thermal conditions, with toluene in a sealed tube at 130 °C and in *o*-dichlorobenzene under reflux (180 °C), gave **4e** (after deprotection with (+)-10-camphorsulfonic acid (CSA)) and **4b** (directly obtained without deprotection procedure) in low yields, respectively (entries 5 and 6). Thirdly, although we used **2c** with a SEM group, which is more stable than a TMS group and less bulky than a TBS group, the thermal conditions gave **4e** whose SEM group was removed in only 12% yield (entry 9). Dienophiles **2a**–**c** have silyloxy protective groups (electron-donating groups) at C3 position. Thus, we prepared **2d** from **2e**, which has an acetoxy group (an electron-withdrawing group) at C3 position because the electronic effect at this position might affect the reactivity of the dienophiles. However, **2d** gave **4d** in low yields under the thermal conditions (entries 12 and 13). Finally, we concluded that the traditional thermal conditions would not give adducts **4** in good yield and that we should discontinue this sequence for the synthesis of **5** and subsequent synthesis of biotin conjugate **6** if improvement on the cycloaddition reactions is not successful.

Although there were not many successful examples of microwave-assisted Diels–Alder reactions using Danishefsky's diene **1**,[16,17] we selected this method for our cycloadditions. Remarkably, under the microwave heating conditions (at 150 °C for 1 h), followed by deprotection with PPTS in THF (at 60 °C) for 2 h, the cycloaddition between **1** and **2a** with *o*-dichlorobenzene or without a solvent gave **4a** in 72% and 87% yields, respectively (entries 3 and 4). In comparison with the thermal conditions, the yield is 1.5–3.5 times higher and the reaction time is 20–48 times shorter. Other dienophiles **2b**–**d** gave the corresponding adducts **4c**–**e** (after deprotection) with a solvent or without a solvent under the microwave conditions (at 150 °C for 1 h) in much better yields (2–7 times) and much shorter times (14–24 times) than the thermal conditions (entries 7, 8, 10, 11, 14, and 15). Importantly, while ethyl α-(hydroxymethyl)acrylate (**2e**) did not give the adduct under the thermal conditions at all (entry 16), **2e** gave the adduct **4e** with *o*-dichlorobenzene under the microwave conditions (at 150 °C for 1 h) in 29% yield (entry 17). Notably, higher temperature conditions with *o*-dichlorobenzene (at 180 °C for 1 h) drastically increased the yield (76%, entry 18). However, under the neat conditions with the microwave heating, no adduct was obtained (entry 19), whilst dienophiles **2a**–**d** gave the adducts in high yield under the same conditions. We speculated that diene **1** might be decomposed under the neat conditions before it gives the adduct with the dienophile **2e** because **2e** is less reactive than other dienophiles (indeed, only **2e** did not give the adduct under the thermal conditions).

3. Conclusion

While the Diels–Alder cycloadditions between Danishefsky's diene **1** and methacrylic acid derivatives **7**, whose structures are similar to those of derivatives of ethyl α-(hydroxymethyl)acrylate **2**, under the traditional thermal conditions gave the adducts **9** in good yields, **1** and **2** gave the adducts only in very low yields. Notably, we found that the microwave heating drastically accelerates the cycloadditions between **1** and dienophiles **2** to give the previously unknown adducts **4**. The reaction time is only 1 h and the average yield is approximately 80%. Compared to the traditional thermal conditions this method requires 1/48th to 1/14th of the time and the yields are 2–7 times more. The synthesis of **5** and **6** using **4a** as the intermediate is in progress.

4. Experimental section

4.1. General procedures

All micro-wave assisted Diels–Alder reactions were carried out in a CEM SP-1372D microwave reactor with an infrared temperature sensor. All NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). The chemical shifts are reported in δ (ppm) using the δ 7.27 signal of $CHCl_3$ (^{1}H NMR) and the δ 77.23 signal of $CDCl_3$ (^{13}C NMR) as internal standards for deuterated chloroform. Coupling constants are reported in hertz (Hz) and the apparent multiplicity is described as s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. High-resolution mass spectroscopy data were obtained by an Agilent 6224AA TOF LC/MS system. Precoated TLC plates with silica gel 60 F_{254} were used for TLC. Flash column chromatography was performed with silica gel (230–400 mesh). All experiments were performed under a nitrogen atmosphere. All solvents (analytical grade) including anhydrous solvents and reagents were used as received. All references to 'water' correspond to reverse osmosis deionized (RODI) water. All references to 'brine' refer to a saturated aqueous sodium chloride solution. The term 'in vacuo' refers to solvent removal by rotary evaporation followed by a lower pressure environment (≤0.2 Torr).

4.2. Ethyl 2-(((2-(trimethylsilyl)ethoxy)methoxy)methyl) prop-2-enoate (2c)

To a solution of ethyl α-(hydroxylmethyl)acrylate (**2e**, 500 mg, 3.9 mmol) and *i*-PrNEt$_2$ (1.4 mL, 7.7 mmol, 2 equiv) in CH_2Cl_2 (61 mL) was added SEMCl (775 mg, 4.7 mmol, 1.2 equiv) in an ice-bath. The mixture was stirred in the ice-bath for 1 h and then at rt for overnight. The reaction was quenched with water (10 mL). The organic phase was washed with brine (10 mL×2), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a residue, which was purified by flash column chromatography [hexane/EtOAc (10:1)] to afford **2e** (1 g, 97%) as a colorless oil: δ_H (400 MHz, $CDCl_3$) 6.30 (d, *J*=1.5 Hz, 1H), 5.86 (d, *J*=1.8 Hz, 1H), 4.73 (s, 2H), 4.29 (t, *J*=1.5 Hz, 2H), 4.25 (q, *J*=7.2 Hz, 2H), 3.64 (m, 2H), 1.3 (t, *J*=7.2 Hz, 3H), 0.95 (m 2H), 0.02 (s, 9H); δ_C (100 MHz, $CDCl_3$) 166.0, 137.6, 126.0, 94.6, 66.0, 65.5, 60.9, 18.3, 14.4, −1.2; HRMS (ESI-TOF) calcd for $C_{12}H_{24}O_4SiNa$ $[M+Na]^+$, 283.1336; found, 283.1340.

4.3. Ethyl 4-oxo-1-(((trimethylsilyl)oxy)methyl)cyclohex-2-enecarboxylate (4b)

A mixture of ethyl 2-(((trimethylsilyl)oxy)methyl)prop-2-enoate (**2b**, 101 mg, 0.5 mmol) and Danishefky's diene (**1**, 103 mg, 0.6 mmol, 1.2 equiv) in *o*-dichlorobenzene (0.5 mL) was heated under reflux (at 180 °C) for 21 h. *o*-Dichlorobenzene was removed in vacuo to give a residue, which was purified by flash column chromatography [hexane/EtOAc (3:1)] on silica gel to give **4b** as an oil (19 mg, 14%): δ_H (400 MHz, $CDCl_3$) 6.94 (d, *J*=9.3 Hz, 1H), 6.12 (d, *J*=10.2 Hz, 1H), 4.24 (m, 2H), 3.85 (d, *J*=11.1 Hz, 1H), 3.79 (d, *J*=11.1 Hz, 1H), 2.48–2.64 (m, 2H), 2.30–2.48 (m, 1H), 2.00–2.20 (m, 1H), 1.29 (t, *J*=6.9 Hz, 3H), 0.07 (s, 9H); δ_C (100 MHz, $CDCl_3$) 198.8, 172.4, 148.8, 130.3, 67.8, 61.6, 50.6, 34.6, 27.9, 14.4, −0.5; HRMS (ESI-TOF) calcd for $C_{13}H_{23}O_4Si$ $[M+H]^+$, 271.1360; found, 271.1361.

4.4. General procedures for microwave-assisted Diels–Alder reactions

A mixture of dienophile **2** (0.5 mmol) and Danishefky's diene (**1**, 103 mg, 0.6 mmol, 1.2 equiv) without a solvent or in *o*-dichlorobenzene (0.5 mL) was heated in the microwave reactor at 150 °C for 1 h. After that, to the reaction mixture (if *o*-dichlorobenzene was used, after it was removed in vacuo) was added THF (5 mL). To the resulting solution was added PPTS (125 mg, 1.37 equiv) or CSA (130 mg, 1.37 equiv). The mixture was heated at 60 °C for 2 h. After the mixture was cooled down, it was diluted with CH_2Cl_2/Et_2O (1:2, 100 mL). The solution was washed with

water (30 mL×2) and brine (30 mL×1), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude adduct **4**.

*4.4.1. Ethyl 1-(((tert-butyldimethylsilyl)oxy)methyl)-4-oxocyclohex-2-enecarboxylate (**4a**).* The crude residue, which was obtained without a solvent in the microwave reactor, was purified by flash column chromatography [hexane/EtOAc (3:1)] on silica gel to give **4a** as an oil (136 mg, 87%): δ_H (400 MHz, $CDCl_3$) 6.99 (d, J=10.2 Hz, 1H), 6.08 (d, J=10.5 Hz, 1H), 4.20 (m, 2H), 3.89 (d, J=9.3 Hz, 2H), 3.74 (d, J=9.3 Hz, 1H), 2.32–2.52 (m, 3H), 2.02 (ddd, J=5.7, 9.6, 13.2 Hz, 1H), 1.28 (t, J=7.2 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); δ_C (100 MHz, $CDCl_3$) 198.9, 172.4, 148.8, 130.3, 68.3, 61.7, 50.8, 34.7, 28.0, 25.8, 18.3, 14.4, −5.5; HRMS (ESI-TOF) calcd for $C_{16}H_{29}O_4Si$ $[M+H]^+$, 313.1830; found, 313.1830. The consistent data of the elemental analysis were obtained after **4a** was converted to **4e** (see the analytical data of **4e** below).

*4.4.2. Ethyl 4-oxo-1-(((2-(trimethylsilyl)ethoxy)methoxy)methyl)cyclohex-2-enecarboxylate (**4c**).* The crude residue, which was obtained without a solvent in the microwave reactor, was purified by flash column chromatography [hexane/EtOAc (3:1)] on silica gel to give **4c** as an oil (136 mg, 82%): δ_H (400 MHz, $CDCl_3$) 6.95 (d, J=10 Hz, 1H), 6.08 (d, J=10 Hz, 1H), 4.66 (s, 3H), 4.21 (q, J=7.2 Hz, 2H), 3.78 (d, J=11.2 Hz, 1H), 3.70 (d, J=11.6 Hz, 1H), 3.58 (m, 2H), 2.38–2.58 (m, 2H), 2.09 (ddd, J=6.4, 11.6, 14.8 Hz, 1H), 1.27 (t, J=7.2 Hz, 3H), 0.93 (m, 2H), 0.17 (s, 9H); δ_C (100 MHz, $CDCl_3$) 198.5, 177.1, 148.3, 130.5, 95.2, 65.6, 61.8, 49.1, 34.6, 28.4, 18.2, 14.4, −1.2; HRMS (ESI-TOF) calcd for $C_{16}H_{28}O_5SiNa$ $[M+Na]^+$, 351.1598; found, 351.1591.

*4.4.3. Ethyl 1-(acetoxymethyl)-4-oxocyclohex-2-enecarboxylate (**4d**).* The crude residue, which was obtained in *o*-dichlorobenzene in the microwave reactor, was purified by flash column chromatography [hexane/EtOAc (4:1)] on silica gel to give **4d** as an oil (103 mg, 85%): δ_H (400 MHz, $CDCl_3$) 6.88 (dd, J=1.2, 10.5 Hz, 1H), 6.12 (d, J=10.2 Hz, 1H), 4.38 (d, J=10.8 Hz, 1H), 4.18–4.28 (m, 3H), 2.40–2.64 (m, 3H), 2.08 (s, 3H), 2.02–2.16 (m, 1H), 1.29 (t, J=7.2 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 197.9, 171.2, 170.4, 146.6, 131.0, 67.6, 62.0, 48.1, 34.2, 28.2, 20.7, 14.2; HRMS (ESI-TOF) calcd for $C_{12}H_{17}O_5$ $[M+H]^+$, 214.1071; found, 214.1073.

*4.4.4. Ethyl 1-(hydroxymethyl)-4-oxocyclohex-2-enecarboxylate (**4e**).* A mixture of ethyl α-(hydroxymethyl)acrylate (**2e**, 65 mg, 0.5 mmol) and Danishefky's diene (**1**, 103 mg, 0.6 mmol, 1.2 equiv) in *o*-dichlorobenzene (0.5 mL) was heated at 180 °C for 1 h in the microwave reactor. After *o*-dichlorobenzene was removed in vacuo, THF (5 mL) was added. To the resulting solution was added PPTS (125 mg, 1.37 equiv). The mixture was heated at 60 °C for 2 h. After the mixture was cooled down, it was diluted with CH_2Cl_2/Et_2O (1:2, 100 mL). The solution was washed with water (30 mL×2) and brine (30 mL×1), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a residue, which was purified by flash column chromatography [hexane/EtOAc (1:1)] on silica gel to give **4e** as an oil (76 mg, 76%). Found: C, 59.80; H, 7.24. $C_{10}H_{14}O_4 \cdot 1/6H_2O$ requires C, 59.69; H, 7.18. δ_H (400 MHz, $CDCl_3$) 6.93 (dd, J=0.9, 10.2 Hz, 1H), 6.13 (d, J=10.2 Hz, 1H), 4.25 (q, J=7.2 Hz, 2H), 3.85 (d, J=10.8 Hz, 1H), 3.79 (d, J=10.8 Hz, 1H), 2.04–2.32 (m, 3H), 2.10 (ddd, J=5.4, 9.6, 13.5 Hz, 1H), 1.94 (brs, 1H), 1.30 (t, J=7.2 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 198.9, 172.9, 148.2, 130.5, 67.1, 61.9, 50.2, 34.2, 27.7, 14.2; HRMS (ESI-TOF) calcd for $C_{10}H_{15}O_4$ $[M+H]^+$, 199.0965; found, 199.0965.

Acknowledgements

We thank Dr. Bela Ruzsicska (Stony Brook University) for expert technical assistance with LC–MS. We also thank Divya Awasthi (Stony Brook University) for technical assistance with microwave reactor. This work was supported by funds from Reata Pharmaceuticals.

Supplementary data

These data include copies of ^1H and ^{13}C NMR for all new compounds described in this article. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.12.079.

References and notes

1. Dinkova-Kostova, A. T.; Talalay, P.; Sharkey, J.; Zhang, Y.; Holtzclaw, W. D.; Xiu Jun Wang, X. J.; David, E.; Schiavoni, K. H.; Finlayson, S.; Mierke, D. F.; Honda, T. *J. Biol. Chem.* **2010**, *285*, 33747–33755.
2. Zheng, S.; Laxmi, Y. R. S.; David, E.; Dinkova-Kostova, A. T.; Shiavoni, K. H.; Ren, Y.; Zheng, Y.; Trevino, I.; Bumeister, R.; Ojima, I.; Wigley, W. C.; James, J. B.; Mierke, D. F.; Honda, T. *J. Med. Chem.* **2012**, *55*, 4837–4846.
3. Honda, T.; Rounds, B. V.; Gribble, G. W.; Suh, N.; Wang, Y.; Sporn, M. B. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2711–2714.
4. Honda, T.; Rounds, B. V.; Bore, L.; Favaloro, F. G., Jr.; Gribble, G. W.; Suh, N.; Wang, Y.; Sporn, M. B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3429–3434.
5. Honda, T.; Rounds, B. V.; Bore, L.; Finlay, H. J.; Favaloro, F. G., Jr.; Suh, N.; Wang, Y.; Sporn, M. B.; Gribble, G. W. *J. Med. Chem.* **2000**, *43*, 4233–4246.
6. Pergola, P. E.; Raskin, P.; Toto, R. D.; Meyer, C. J.; Huff, J. W.; Grossman, E. B.; Krauth, M.; Ruiz, S.; Audhya, P.; Christ-Schmidt, H.; Wittes, J.; Warnock, D. G. *N. Engl. J. Med.* **2011**, *365*, 327–336.
7. Honda, T.; Sundararajan, C.; Yoshizawa, H.; Su, X.; Honda, Y.; Liby, K. T.; Sporn, M. B.; Gribble, G. W. *J. Med. Chem.* **2007**, *50*, 1731–1734.
8. Honda, T.; Yoshizawa, H.; Sundararajan, C.; David, E.; Lajoie, M. j.; Favaloro, F. G., Jr.; Janosik, T.; Su, X.; Honda, Y.; Roebuck, B. D.; Gribble, G. W. *J. Med. Chem.* **2011**, *54*, 1762–1778.
9. Honda, T.; Janosik, T.; Honda, Y.; Han, J.; Liby, K. T.; Williams, C. R.; Couch, R. D.; Anderson, A. C.; Sporn, M. B.; Gribble, G. W. *J. Med. Chem.* **2004**, *47*, 4923–4932.
10. Ahmad, R.; Raina, D.; Meyer, C.; Kharbanda, S.; Kufe, D. *J. Biol. Chem.* **2006**, *281*, 35764–35769.
11. Ahmad, R.; Raina, D.; Meyer, C.; Kufe, D. *Cancer Res.* **2008**, *68*, 2920–2926.
12. Miyata, J.; Nemoto, H.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 504–512.
13. De la Hoz, A.; Diaz-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3659–3673.
14. Pineiro, M.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2009**, 5287–5307.
15. Appukkuttan, P.; Mehta, V. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2010**, *39*, 1467–1477.
16. For a review of the microwave-assisted organic synthesis see: Kappe, C. O.; Stadler, A.; Dallinger, D. Diels–Alder Reactions In *Microwaves in Organic and Medicinal Chemistry*, 2nd ed.; Mannhold, R., Kubinyi, H., Folkers, G., Eds.; Methods and Principles in Medicinal Chemistry; Wiley-VCH: Weinheim, Germany, 2012; Vol. 52, Chapter 2, Microwave theory, pp 9–40 and Chapter 6.2.1, Diels–Alder reactions, pp 309–318.
17. For example: Burland, P. A.; Coisson, D.; Osborn, H. M. I. *J. Org. Chem.* **2010**, *75*, 7210–7218.
18. Crimmins, M. T.; Jacobs, D. L. *Org. Lett.* **2009**, *11*, 2695–2698.
19. Amri, H.; Rambaud, M.; Villieras, J. *J. Organomet. Chem.* **1990**, *384*, 1–11.
20. Huang, H.; Liu, X.; Deng, J.; Qiu, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359–3362.
21. Kippo, T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2011**, *13*, 3864–3867.