Tetrahedron Letters 54 (2013) 4817–4820

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Synthetic studies towards tragoponol: preparation of a highly functionalized resorcylate

Hideki Miyatake-Ondozabal, Anthony G. M. Barrett *

Department of Chemistry, Imperial College, England SW7 2AZ, London

ARTICLE INFO

Article history:
Received 12 March 2013
Accepted 10 May 2013
Available online 17 May 2013

Keywords:
Resorcylic acid lactones
Resorcylate unit
Retro-Diels–Alder
Intermolecular ketene trapping
Diketo-dioxinones

ABSTRACT

Studies on the synthesis of racemic tragoponol are described. The western resorcylate unit of tragoponol was efficiently constructed from appropriate diketo-dioxinone and secondary alcohol intermediates using a ketene generation–trapping and aromatization sequence. Further functionalization provided an advanced diketo-dioxinone intermediate which upon desilylation resulted in the formation of a dihydroisocoumarin.

© 2013 Elsevier Ltd. All rights reserved.

Numerous bioactive natural products, including resorcylic acid lactones (RALs), contain a key 6-alkyl-2,4-dihydroxybenzoic ester unit.[1] Two examples are shown in Figure 1, the antifungal agent 15G256β (**1**)[2] and the TAK-kinase inhibitor LL-Z1640-2 (**2**).[3] Due to their notable biological activities, these natural products have been the subject of extensive synthetic studies. In 2008, inspired by the earlier work of Harris,[4] Hyatt[5] and Boeckmann,[6] the first biomimetic synthesis of 15G256β (**1**)[7] was completed. The methodology, based on the use of diketo-dioxinones,[8] was extended to other macrocyclic lactones by intermolecular ketene trapping including cruentaren A,[9] the fungal metabolites W1278A–C[10] and aigialomycin D,[11] and by intramolecular trapping and concurrent macrocyclization applied to the total syntheses of (−)-zearalenone[12] and LL-Z1640-2 (**2**).[13] Tragoponol (**3**) represents the first dimeric dihydroisocoumarin isolated from the roots of *Tragopon porrifolius* by Zidorn and co-workers in 2010.[14] This natural product consists of a novel 12-membered dilactone system and it can also be recognized as an unsymmetrical resorcylic dimer (Fig. 1). The monomeric subunits of tragoponol (**3**) are found in other natural products including scorzocreticin (**4**),[15] thunberginol C (**5**)[16] and hongkongenin (**6**),[17] which are known to possess anti-allergic, anti-microbial and anti-oxidant activities. The biological activity of tragoponol (**3**) has not yet been investigated in detail. To date, no total synthesis of **3** has been reported.

Herein we report our studies towards the synthesis of racemic tragoponol (**3**) and its racemic diastereoisomer using a ketene-generation, trapping and aromatization sequence. The retrosynthetic analysis is shown in Scheme 1.

Following our successful total synthesis of LL-ZI640-2 (**2**) which employed macrocyclization by intramolecular ketene trapping with an alcohol,[13] we considered that tragoponol (**3**) should be available from hydroxy-diketo-dioxinone **7** by an equivalent trapping and subsequent transannular aromatization and regioselective demethylation. Dioxinone **7** should be available from Weinreb amide **8** via C-acylation of keto-dioxinone and desilylation. We sought to synthesize the western resorcylate part of **8** by thermolysis of diketo-dioxinone **9** in the presence of secondary

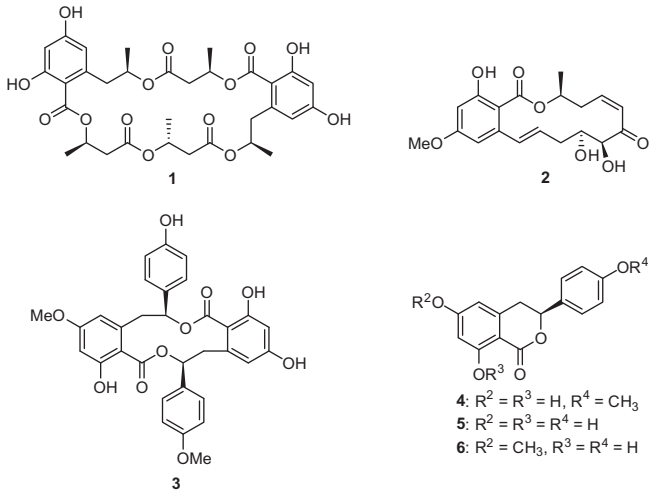
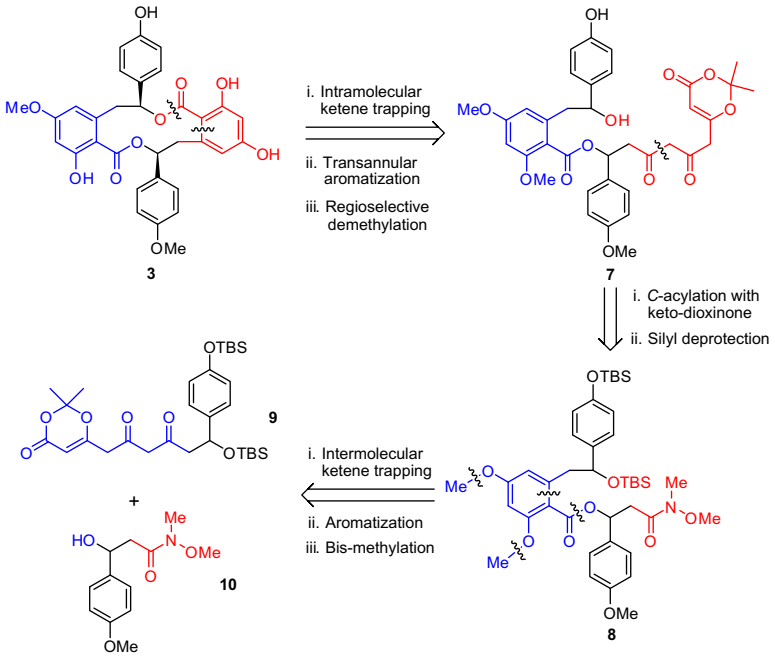


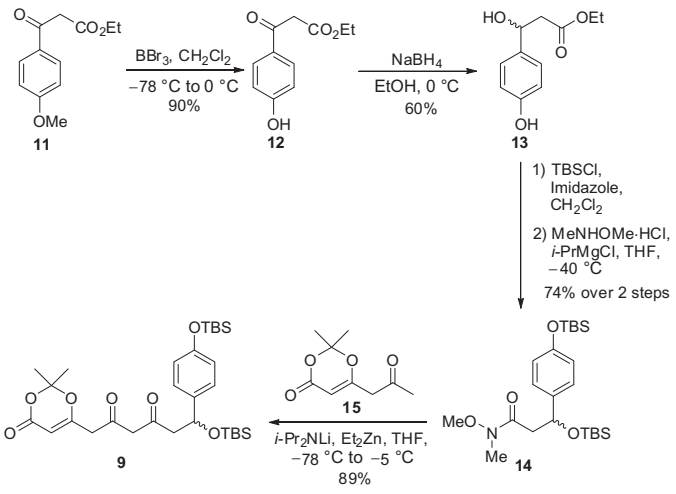
Figure 1. 15G256β (**1**), LL-Z1640-2 (**2**), tragoponol (**3**), scorzocreticin (**4**), thunberginol C (**5**) and hongkongenin (**6**).

* Corresponding author. Tel.: +44 020 7594 5766; fax: +44 020 7594 5805.
E-mail address: agm.barrett@imperial.ac.uk (A.G.M. Barrett).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.05.044



Scheme 1. Retrosynthetic analysis of tragoponol (**3**).



Scheme 2. Synthesis of diketo-dioxinone **9**.

alcohol **10** to give the triketo-ester intermediate, which in turn should aromatize to give our target molecule. Bis-methylation of the resulting resorcinol unit should provide intermediate **8**.

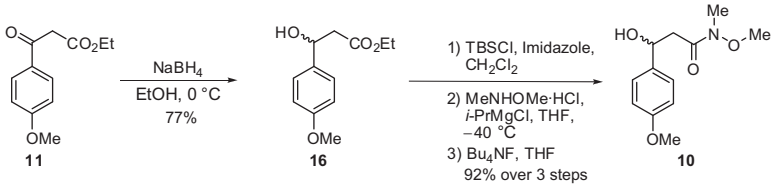
The synthesis of diketo-dioxinone **9** was achieved in five-steps from commercially available starting materials (Scheme 2). β-Ketoester **11** was allowed to react with boron tribromide to provide phenol **12**[18] in 90% yield, which was reduced with sodium borohydride to give the corresponding alcohol **13**.[19] Following *t*-butyldimethyldisilylation, the carboxylic ester was converted into Weinreb amide **14** in 74% yield, using *iso*-propylmagnesium chloride and *N*,*O*-dimethylhydroxylamine. Reaction of the zinc enolate dianion,[13,20,21] derived from keto-dioxinone **15**[20] with lithium di-*iso*-propylamide and diethylzinc, and Weinreb amide **14** gave diketo-dioxinone 9 in excellent yield and in gram quantities.[22]

β-Ketoester **11** was allowed to react with sodium borohydride to give alcohol **16**[23] in 77% yield. Following *t*-butyldimethylsilylation, Weinreb amide formation and tetrabutylammonium fluoride mediated desilylation gave hydroxamate **10**[24] in 92% yield over three-steps (Scheme 3).

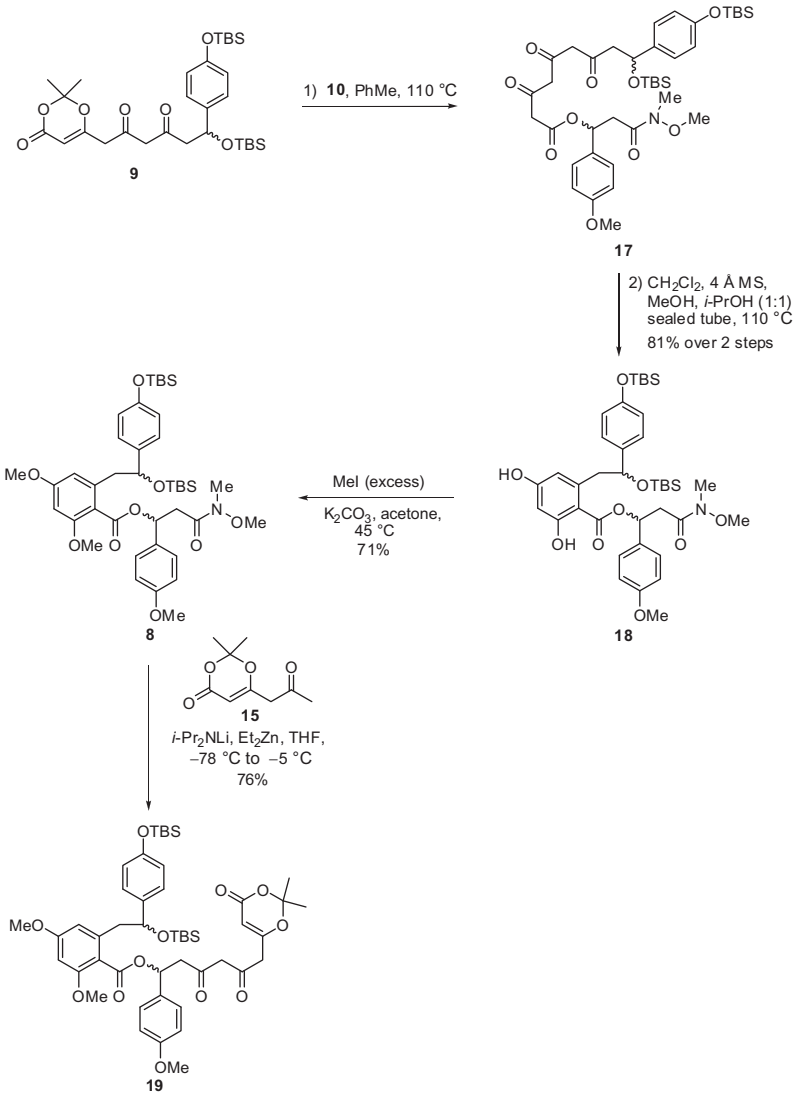
As expected, thermolysis of diketo-dioxinone **9** resulted in retro–hetero-Diels–Alder fragmentation[5] to generate the diketo-ketene intermediate, which was efficiently trapped in situ by alcohol **10** to provide triketo-ester **17** (Scheme 4). Subsequent aromatization at elevated temperature yet under mild conditions[25] gave resorcylate **18** in 81% yield over two-steps. It is noteworthy that the use of both methanol and *iso*-propanol (1:1 mixture) was crucial for obtaining a high yield in this transformation. A significant amount of transesterified byproduct was observed in the absence of *iso*-propanol, whereas the reaction was extremely slow and low yielding when performed solely in *iso*-propanol.

Diol **18** was dimethylated by reaction with excess methyl iodide in the presence of potassium carbonate to furnish resorcylate **8** in 71% yield (Scheme 4). Subsequent addition of the zinc enolate dianion,[13,20,21] derived from dioxinone **15**, to **8** proceeded smoothly to yield diketo-dioxinone **19** (76%).

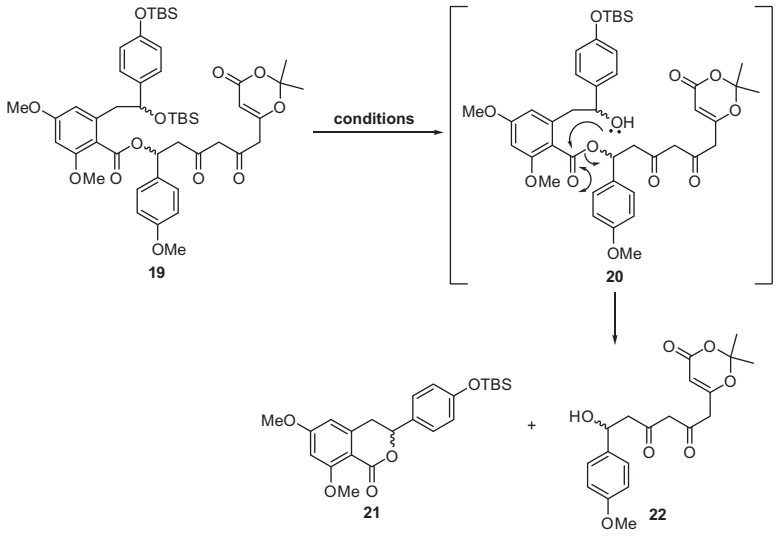
The projected final steps included secondary alcohol silyl ether deprotection followed by intramolecular ketene trapping and transannular aromatization to produce the macrocyclic bis-resorcylate. A range of conditions was screened for the desi-



Scheme 3. Synthesis of alcohol **10**.



Scheme 4. Synthesis of resorcylate **18** and diketo-dioxinone **19**.



Scheme 5. Six-membered lactonization of **20** to form dihydroisocoumarin **21**.

lylation step (Scheme 5). The use of hydrogen fluoride initially gave the desired product **20**, however rapid δ-lactonization gave dihydroisocoumarin **21** in quantitative yield. Dioxinone **22** decomposed during attempted purification. Deprotection of the silyl ether **19** was examined using zirconium tetrachloride, which resulted in the recovery of unreacted starting material **19**. Tetrabutylammonium fluoride mediated selective deprotection of the aryl silyl ether. Finally, desilylation with hexafluorosilicic acid did result in completely selective secondary silyl ether deprotection. However upon work-up, rapid δ-lactonization again could not be suppressed and only isochromanone **21** was isolated. All efforts to induce ketene generation during silyl deprotection to trigger the desired cyclization also failed to produce the triketo-ester-macrocycle. It is noteworthy that δ-lactonization during the synthesis of W1278A–C[10] could be significantly suppressed and the total synthesis completed. Presumably the 16-membered macrocyclic triketo-lactone from alcohol **20** was formed at too slow a rate to overcome competition from δ-lactonization.

In conclusion, attempted macrocyclization of the triketo-ketene derived from dioxinone **20** was less efficient than fragmentation via a δ-lactonization pathway. It is noteworthy that the study did provide the polyfunctional resorcylate **19** in 13 steps and with an overall yield of 11%. The key transformations in its synthesis were the mild aromatization of triketo-ester **17**–**18** under neutral conditions and the late-stage incorporation of keto-dioxinone unit **15** via dianion addition to Weinreb amide **8**.

Acknowledgments

We thank P.R. Haycock and R.N. Sheppard (Imperial College London) for help with high-resolution NMR spectroscopy and the Engineering and Physical Sciences Research Council (EPSRC) for financial support (to H.M.O.). We also thank Professor Dr. Christian Zidorn (University of Innsbruck) for kindly providing us with an authentic sample of tragoponol.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.044.

References and notes

1. Winssinger, N.; Barluenga, S. *Chem. Commun.* **2007**, 22.
2. Schlingmann, G.; Milne, L.; Carter, G. T. *Tetrahedron* **2002**, *58*, 6825. and references therein.
3. (a) Schirmer, A.; Kennedy, J.; Murli, S.; Reid, R.; Santi, V. D. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 4234; (b) Dakas, P. Y.; Barluenga, S.; Totzke, F.; Zirrgiebel, U.; Winssinger, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 6899.
4. Harris, T. M.; Harris, C. M. *Tetrahedron* **1977**, *33*, 2159.
5. Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, *49*, 5105.
6. (a) Boeckman, R. K., Jr.; Shao, P.; Wrobleski, S. T.; Boehmler, D. J.; Heintzelman, G. R.; Barbosa, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 10572; (b) Boeckman, R. K., Jr.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486; (c) Boeckman, R. K., Jr.; Starrett, J. E., Jr.; Nickell, D. G.; Sum, P.-E. *J. Am. Chem. Soc.* **1986**, *108*, 5549.
7. Navarro, I.; Basset, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Brackow, J.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2008**, *130*, 10293.
8. For the use of diketo-dioxinones in natural product synthesis, see: (a) Anderson, K.; Calo, F.; Pfaffeneder, T.; White, A. J. P.; Barrett, A. G. M. *Org. Lett.* **2011**, *13*, 5748; (b) Cordes, J.; Laclef, S.; White, A. J. P.; Barrett, A. G. M. *J. Org. Chem.* **2012**, *77*, 3524.
9. Fouché, M.; Rooney, L.; Barrett, A. G. M. *J. Org. Chem.* **2012**, *77*, 3060.
10. Navarro, I.; Pöverlein, C.; Schlingmann, G.; Barrett, A. G. M. *J. Org. Chem.* **2009**, *74*, 8139.
11. Calo, F.; Richardson, J.; Barrett, A. G. M. *Org. Lett.* **2009**, *11*, 4910.
12. Miyatake-Ondozabal, H.; Barrett, A. G. M. *Tetrahedron* **2010**, *66*, 6331.
13. Miyatake-Ondozabal, H.; Barrett, A. G. M. *Org. Lett.* **2010**, *12*, 5573.
14. Zidorn, C.; Petersen, B. O.; Sareedenchai, V.; Ellmerer, E. P.; Duus, J. Ø. *Tetrahedron Lett.* **2010**, *51*, 1390.
15. Paraschos, S.; Magiatis, P.; Kalpoutzakis, E.; Harvala, C.; Skaltsounis, A.-L. *J. Nat. Prod.* **2001**, *64*, 1585.
16. Yoshikawa, M.; Uchida, E.; Chantani, N.; Kobayashi, H.; Naitoh, Y.; Okuno, Y.; Matsuda, H.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1992**, *40*, 3352.
17. Wu, J.-F.; Chen, S.-B.; Gao, J.-C.; Song, H.-L.; Wu, L.-J.; Chen, S.-L.; Tu, P.-F. *Nat. Prod. Res.* **2007**, *21*, 580.
18. Pidathala, C.; Amewu, R.; Pacorel, B.; Nixon, G. L.; Gibbons, P.; Hong, W. D.; Leung, S. C.; Berry, N. G.; Sharma, R.; Stocks, P. A.; Srivastava, A.; Shone, A. E.; Charoensutthivarakul, S.; Taylor, L.; Berger, O.; Mbekeani, A.; Hill, A.; Fisher, N. E.; Warman, A. J.; Biagini, G. A.; Ward, S. A.; O'Neill, P. M. *J. Med. Chem.* **1831**, *2012*, 55.
19. Miura, K.; Nakagawa, T.; Hosomi, A. *Synlett* **2005**, 1917.
20. For the improved synthesis of keto-dioxinone **15**, see: Patel, B. H.; Mason, A. M.; Patel, H.; Coombes, R. C.; Ali, S.; Barrett, A. G. M. *J. Org. Chem.* **2011**, *76*, 6209.
21. Patel, B. H.; Heath, S. F. A.; Mason, A. M.; Barrett, A. G. M. *Tetrahedron Lett.* **2011**, *52*, 2258.
22. All the diketo-dioxinones and triketo-esters exist as mixtures of keto and enol tautomers. However, for convenience, they are drawn as single entities.
23. Wan, X.; Sun, Y.; Luo, Y.; Li, D.; Zhang, Z. *J. Org. Chem.* **2005**, *1070*, 70.
24. Andrés, J. M.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron* **2000**, *56*, 1217.
25. Basset, J.-F.; Leslie, C.; Hamprecht, D.; White, A. J. P.; Barrett, A. G. M. *Tetrahedron Lett.* **2010**, *51*, 783.