Tetrahedron Letters 51 (2010) 86–88

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Rapid annulation of tropolone units via a pyrylium ylide 1,3-dipolar cycloaddition reaction

Kirill Tchabanenko *, Peter McIntyre, John F. Malone

School of Chemistry and Chemical Engineering, Queens University, David Keir Building, Stranmillis Road, Belfast, BT9 5AG, United Kingdom

ARTICLE INFO

Article history:
Received 13 July 2009
Revised 13 October 2009
Accepted 19 October 2009
Available online 22 October 2009

ABSTRACT

The tropolone subunit of the naturally occurring alkaloid rubrolone aglycon is synthesized via a short reaction sequence starting with a 1,3-dipolar cycloaddition of a pyrylium ylide and indenone, followed by enone oxidation, oxygen-bridge elimination and finally hydroxy group oxidation.

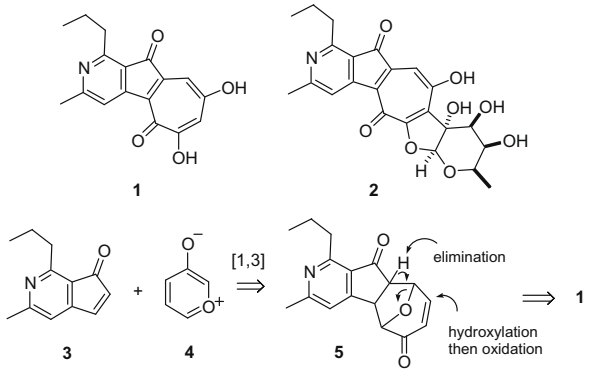
1,3-Dipolar cycloaddition of pyrylium ylides is a versatile method for the construction of seven-membered rings,[1,2] which has been widely applied in total syntheses of natural products.[3] One class of compounds which can be easily accessed via this methodology is tropolones.[4] Our interest in developing further applications of this powerful reaction led to the identification of a new target—rubrolone aglycon (**1**),[5,6] which along with a number of structurally related natural products such as rubrolone (**2**)[7] contains a unique azuleno[2,3-*c*]pyridine-2,5,13-trione subunit. In addition to the establishment of a short synthetic pathway to the tropolene unit of **1**, we have also investigated pyrylium ylide cycloadditions with bicyclic polarophiles, which lead to direct syntheses of complex polycyclic structures.

Our strategy towards direct construction of the tropolone unit of **1** is presented in Scheme 1. Condensation of a known [2]pyrindin-7-one (**3**)[8] with pyrylium ylide **4** would produce the seven-membered ring in compound **5**. Conjugated hydroxylation, oxygen-bridge elimination and final oxidation would result in a short approach to rubrolone aglycon (**1**). The established methodology should be applicable to a wide range of tropolone-containing natural products.

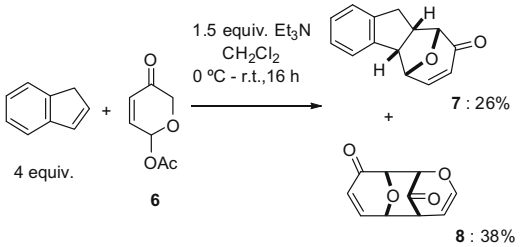
To test this proposal the 1,3-dipolar cycloaddition of pyranyl acetate **6**[1] with commercially available indene[9] was investigated (Scheme 2). When pyranyl acetate **6** was added slowly to a solution of 4 equiv of indene and 1.5 equiv of triethylamine in dichloromethane, the reaction gave exclusively the *endo* cycloadduct **7** along with a significant amount of pyrylium dimer **8**[2] (Scheme 2).

Formation of the dimer **8**, even in the presence of excess indene, suggests its low activity as a polarophile, which also contributes to the high selectivity of the cycloaddition. The cycloadduct **7** is notably a regioisomer of the proposed intermediate **5**, but it was expected that the presence of a carbonyl group in the next model polarophile—indenone[10] would lead to a reversal of the cycloaddition pathway.

The higher reactivity of indenone as a polarophile required a change in the reaction conditions. Cycloaddition (Scheme 3) was best carried out by a rapid addition of triethylamine to a dichloromethane solution of pyranyl acetate **6** and 1.4 equiv of indenone at 0 °C, then allowing the reaction to warm and stir for an additional 4 h, after which TLC indicated complete consumption of the start-



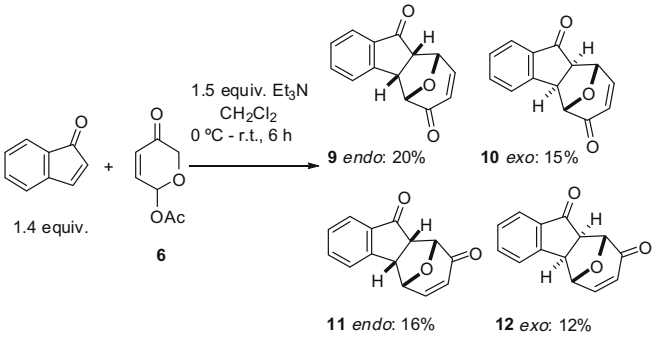
Scheme 1. Tropolone natural products and synthetic strategy.



Scheme 2. Cycloaddition with indene.

* Corresponding author.
E-mail address: k.tchabanenko@qub.ac.uk (K. Tchabanenko).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.10.081



Scheme 3. Cycloaddition with indenone.

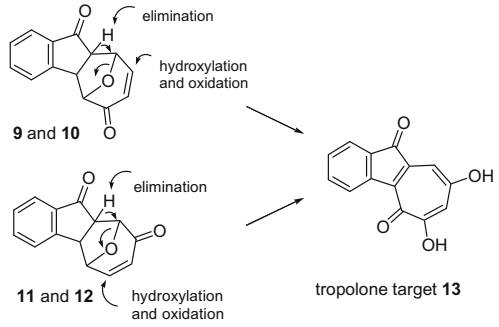


Figure 2. Similar synthetic strategies for both regioisomers.

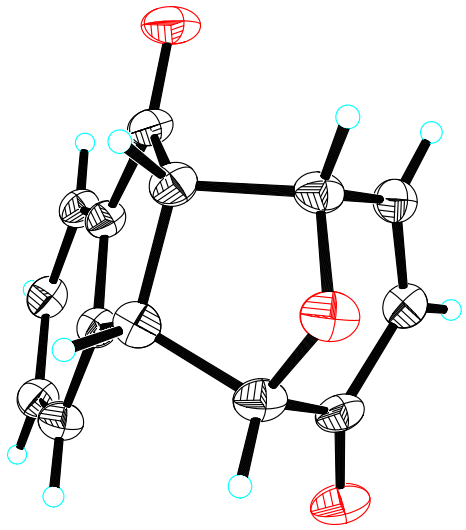
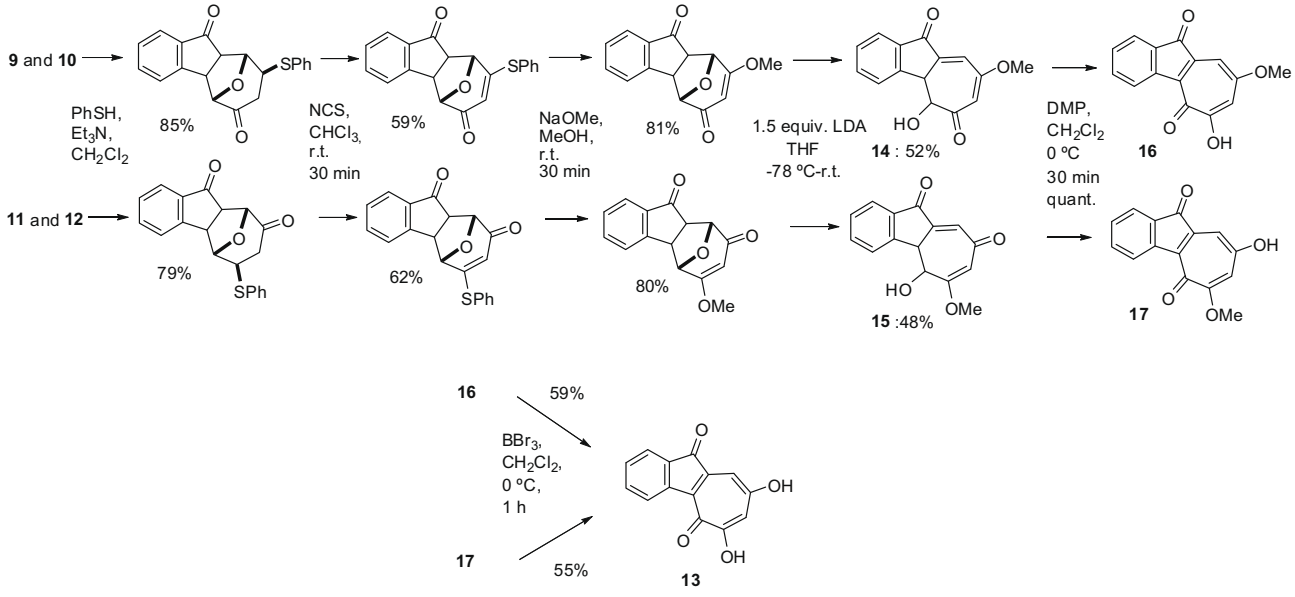


Figure 1. ORTEP plot of the X-ray structure of **9**.

ing material. No pyrylium dimer **8** was formed this time, but the reaction produced four products—*exo* and *endo* stereoisomers of both regioisomeric adducts. We were able to separate a small amount of isomer **9**, and its structure was determined by single crystal X-ray analysis (Fig. 1).[11] Correlation of the NMR data of the other isomeric compounds with **9** allowed us to determine the structures of all four cycloadducts as presented in Scheme 3.

At this point it was noticed that all four of the cycloadducts could be converted into the same target molecule **13** if the elimination of the oxygen bridge was assisted by the five-membered ring carbonyl ($E1_{cb}$) in both regioisomers (Fig. 2). Thus, taking into account that the overall yield of the adducts was a satisfactory 63%, we decided to proceed with all four compounds. Column chromatography allowed separation of the regioisomeric pairs and subsequent reactions were performed on the mixtures of *exo* and *endo* isomers of each regioisomeric compound separately.

We chose to use Pummerer chemistry to oxidize the β-positions of the enones following a literature example.[12] Conjugate addition of thiophenol proceeded in good yields with high diastereoslectivity giving a single product from each cycloadduct (Scheme 4). Pummerer rearrangement of the resulting sulfides was effected using 3 equiv of *N*-chlorosuccinimide in chloroform and substitution of the thiophenyl group for methoxy was accomplished on treatment of the oxidation products with freshly prepared sodium methoxide in methanol. Oxygen-bridge elimination proceeded with anticipated regioselectivity on treatment of the compound mixtures with 1.5 equiv of lithium diisopropylamide in tetrahydrofuran at −78 °C and slow warming of the reaction mixtures to room temperature. Oxidation of the liberated hydroxy groups with Dess–Martin reagent led to regioisomerically methylated tropolones **16** and **17** (Scheme 4). Finally, boron tribromide cleavage of



Scheme 4. Completion of the synthesis of the model compound **13**.

the methyl ethers[13] in both **16** and **17** led to formation of the target tropolone product **13**. Compound **13** was previously reported by Boger et al. and confirmation of the final structure was possible by comparison of the proton and carbon NMR data of our sample in deuterated methanol with those published.[14] At this point we would like to note that the tautomeric form of the tropolone unit in **13** cannot be assigned with certainty based on the NMR data and we chose the presentation closest to the structure of the tropolone unit in rubrolone **1**.

In conclusion, we have described an annulation approach for direct installation of a tropolone unit of rubrolone aglycon utilizing a 1,3-dipolar cycloaddition of a pyrylium ylide. This general method based on condensation of pyrylium ylides with enones followed by oxygen-bridge elimination and aromatizing oxidation of the liberated hydroxy function should be applicable to the synthesis of a wide range of tropolone-containing natural products.

Acknowledgements

We are grateful to Professor Sir Jack E. Baldwin for original expertise in the field, and would like to acknowledge the ASEP staff of the School of Chemistry for their help with structure determinations and Queen's University, Belfast, for support.

References and notes

1. Original report of a high temperature reaction: Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3359.
2. Triethylamine-promoted reactions: Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3361; Sammes, P. G.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1261; Sammes, P. G.; Street, L. J. *Chem. Commun.* **1983**, 666.
3. Applications in total synthesis: Marshall, K. A.; Mapp, A. K.; Heathcock, C. H. *J. Am. Chem. Soc.* **1996**, *61*, 9135; Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954; Williams, D. R.; Benbow, J. W.; McNutt, J. G.; Allen, S. E. *J. Org. Chem.* **1995**, *60*, 833; Magnus, P.; Diorazio, L.; Donohoe, T. J.; Giles, M.; Pye, P.; Tarrant, J.; Thom, S. *Tetrahedron* **1996**, *52*, 14147; Snider, B. B.; Grabowski, J. F. *Tetrahedron* **2006**, *62*, 5171; Tang, B.; Bray, C. D.; Pattenden, G. *Tetrahedron. Lett.* **2006**, *47*, 6401; Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett.* **2006**, *8*, 5901; Snider, B. B.; Wu, X.; Nakamura, S.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 873.
4. Previous synthesis of tropolone natural products: Adlington, R. M.; Baldwin, J. E.; Mayweg, A. V. W.; Pritchard, G. J. *Org. Lett.* **2002**, *4*, 3009.
5. Schuep, W.; Blount, J. F.; Williams, T. H.; Stempel, A. *J. Antibiot.* **1978**, *31*, 1226.
6. Previous total syntheses of rubrolone aglycon: Kelly, T. R.; Echavarren, A.; Whiting, A.; Weibel, F. R.; Miki, Y. *Tetrahedron Lett.* **1986**, *27*, 6049; Boger, D. L.; Ichikawa, S.; Jiang, H. *J. Am. Chem. Soc.* **2000**, *122*, 12169.
7. Palleroni, N. J.; Reichelt, K. F.; Mueller, D.; Epps, R.; Tabenkin, B.; Bull, D. N.; Schuep, W.; Berger, J. *J. Antibiot.* **1978**, *31*, 1218.
8. Kelly, T. R.; Liu, H. *J. Am. Chem. Soc.* **1985**, *107*, 4998; Boger, D. L.; Zhu, Y. *Tetrahedron Lett.* **1991**, *32*, 7643.
9. This reaction was previously reported: Krishna, U. M.; Trivedi, G. K. *Tetrahedron Lett.* **2004**, *45*, 257.
10. Indenone was prepared following the reported procedure: Zengin, M.; Dastan, A.; Balci, M. *Synth. Commun.* **2001**, *31*, 1993.
11. *Crystal data for* **9**: $C_{14}H_{10}O_3$, $M = 226.2$, monoclinic, $a = 10.970(2)$, $b = 9.545(2)$, $c = 11.596(4)$ Å, $\beta = 117.46(2)^\circ$, $U = 1077.3(4)$ Å^3, $T = 293(2)$ K, Mo-Kα radiation, $\lambda = 0.71069$ Å, space group $P2_1/n$ (no. 14), $Z = 4$, $F(0\,0\,0) = 472$, $D_x = 1.395$ g cm^{-3}, $\mu = 0.10$ mm^{-1}, Bruker P4 diffractometer, ω scans, $4.2^\circ < 2\theta < 55.0^\circ$, measured/independent reflections: 3104/2403, direct methods solution, full matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; hydrogens located in a difference Fourier synthesis but included at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. Final $R_1 = 0.074$ for 1354 data with $F_o > 4\sigma(F_o)$, 155 parameters, $\omega R_2 = 0.272$ (all data), GoF = 1.10, $\Delta\rho_{min,max} = -0.33/0.26$ e Å^{-3}. CCDC 739169.
12. Desmaeele, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292.
13. Detterbeck, R.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 343.
14. Boger, D. L.; Zhu, Y. *J. Org. Chem.* **1994**, *59*, 3453.