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New Approach to 2-Quinolinones

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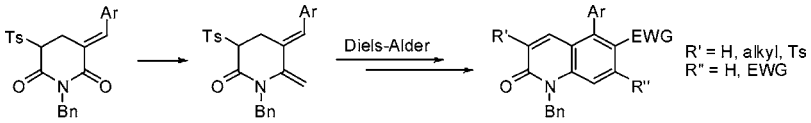
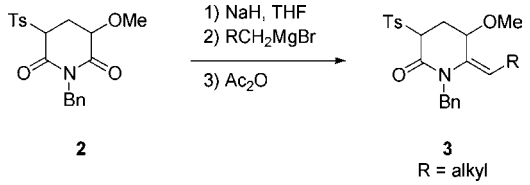
ABSTRACT



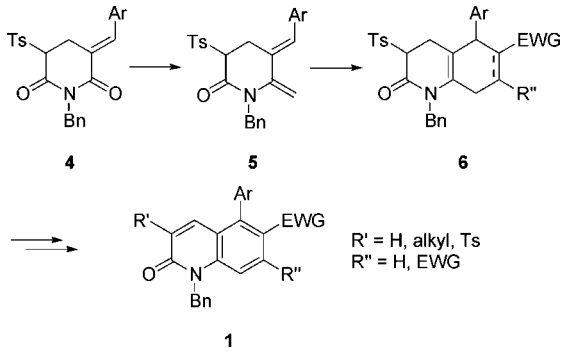
An efficient approach to 2-quinolinone derivatives 1 via Diels–Alder cyclization of *exo*-diene lactams 5 and dienophiles is reported.

Polysubstituted quinolinones, dihydroquinolines, tetrahydroquinolines, and quinolines are common motifs found in natural products and pharmaceutical agents.[1] Furthermore, 2-quinolinone derivatives have been paid considerable attention in organic chemistry due to their use as anti-inflammatories, antihypertensives, and analgesics[2] and in the preparation of antipsychotic agents.[3] As such, a common cascade route to each class of compounds would be of significant synthetic value.

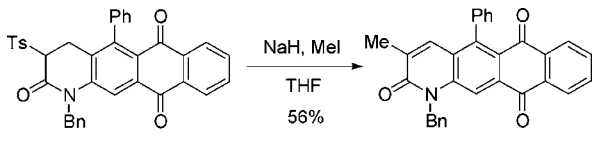
Scheme 1



Scheme 2



Scheme 3



(1) For examples, see the following. Quinolin-2-ones: (a) Carling, R. W.; Leeson, P. D.; Moore, K. W.; Smith, J. D.; Moyes, C. R.; Mawer, I. M.; Thomas, S.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, I. M.; Marshall, G. R.; Tricklebank, M. D.; Saywell, K. L. *J. Med. Chem.* **1993**, *36*, 3397. (b) Rowley, M.; Kulagowski, J. J.; Watt, A. P.; Rathbone, D.; Stevenson, G. I.; Carling, R. W.; Baker, R.; Marshell, G. R.; Kemp, J. A.; Foster, A. C.; Grimwood, S.; Hargreaves, R.; Hurley, C.; Saywell, K. L.; Tricklebank, M. D.; Leeson, P. D. *J. Med. Chem.* **1997**, *40*, 4053. (c) Foucaud, B.; Laube, B.; Schemm, R.; Kreimeyer, A.; Goeldner, M.; Betz, H. *J. Biol. Chem.* **2003**, *278*, 24011. Tetrahydroquinolines: (d) Katritzky, A.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031. Dihydroquinolines: (e) Michne, W. F.; Guiles, J. W.; Treasurywala, A. D.; Castonguay, L. A.; Weigelt, C. A.; Oconnor, B.; Volberg, W. A.; Grant, A. M.; Chadwick, C. C.; Krafte, D. S.; Hill, R. J. *J. Med. Chem.* **1995**, *38*, 1877. (f) Gaillard, S.; Papamicael, C.; Marsais, F.; Dupas, G.; Levacher, V. *Synlett* **2005**, 441. (g) van Straten, N. C. R.; van Berkel, T. H. J.; Demont, D. R.; Karstens, W.-J. F.; Merkx, R.; Oosterom, J.; Schulz, J.; van Someren, R. G.; Timmers, C. M.; van Zandvoort, P. M. *J. Med. Chem.* **2005**, *48*, 1697. Quinolines: (h) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 476.

(2) Setoguchi, N.; Takano, Y. Ch. Kitami. Jpn. Kokai Tokkyo Koho: JP 01006269A2, Jan 1989.

(3) Howard, H. R. Eur. Pat. Appl. EP 409,435 (Cl. C07D403 14).

10.1021/ol7030312 CCC: $40.75
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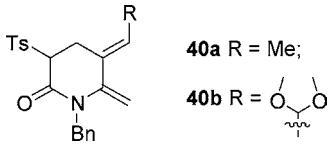
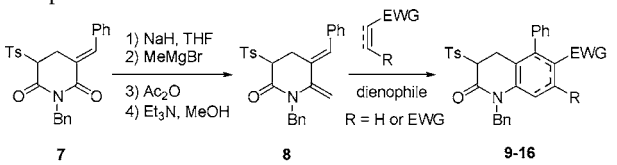
Scheme 4



Although many methods have been developed for the synthesis of quinolines and their derivatives, most are not fully satisfactory either with regard to yield or reaction conditions, generality, or operational simplicity.[4] Therefore, the development of novel synthetic approaches remains an active research area.[5] 2-Quinolinones, reasonable precursors of quinoline, are useful intermediates in organic synthesis.[6] In general, the synthesis of quinolinone starts with benzene and then builds up to the second ring. Following this strategy, the presence of deactivated electron-withdrawing substituents at benzene ring normally will give low yields of quinolinone.

Table 1. Diels−Alder Reaction of Diene **8** with Various Dienophiles



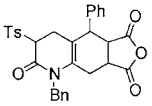
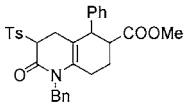
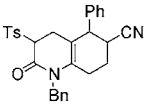
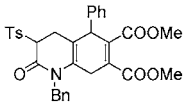
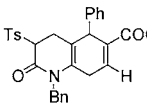
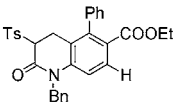
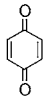
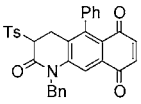
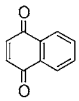
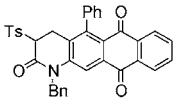
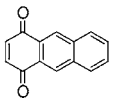
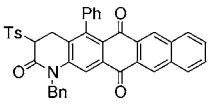
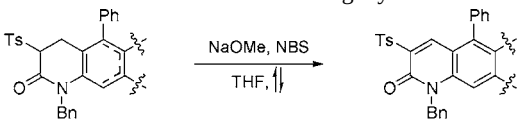
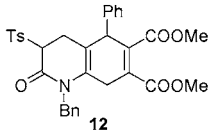
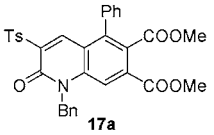
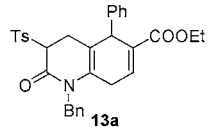
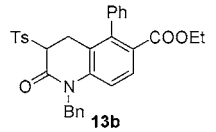
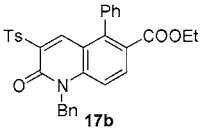
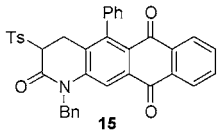
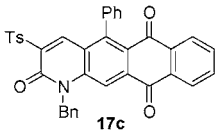
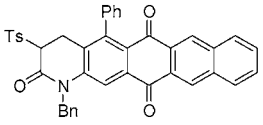
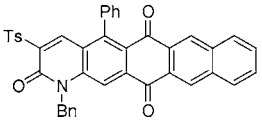
entry	dienophile	products		yield %
1			**9**	66
2			**10**	70
3			**11**	79
4			**12**	74
5		 + 	**13a** / **13b**	64 **13a / 13b** 2 / 1
6			**14**	70
7			**15**	84
8			**16**	80

Table 2. Aromatization of the Resulting Cycloadducts



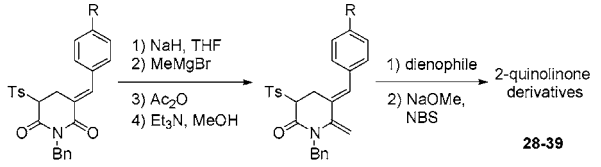
entry	enlactams	2-quinolinones	yield%
1	 **12**	 **17a**	70%
2	 **13a**  **13b**	 **17b**	50%
3	 **15**	 **17c**	42%
4	 **16**	 **17d**	60%

(4) (a) Cho, C. S.; Oh, B. H.; Shim, S. C. *Tetrahedron Lett.* **1999**, *40*, 1499. (b) Zhou, L.; Zhang, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2899. (c) Larock, R. C.; Kero, M.-Y. *Tetrahedron Lett.* **1991**, *32*, 569. (d) Zhou, L.; Tu, S.; Shi, D.; Dai, G.; Chen, W. *Synthesis* **1988**, 851. (e) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291. (f) Ozawa, F.; Yanagihara, H.; Yamamoto, A. *J. Org. Chem.* **1986**, *51*, 415.

(5) Wang, G. W.; Jia, C. S.; Dong, Y. W. *Tetrahedron Lett.* **2006**, *47*, 1059.

(6) (a) Holzapfel, C. W.; Dwyer, C. *Heterocycles* **1998**, *48*, 215. (b) Cortese, N. A.; Ziegler, C. B.; Hrnjez, B. J.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2952. (c) Chorbadjiev, S. *Synth. Commun.* **1990**, *20*, 3497. (d) Kobayashi, K.; Kitamura, T.; Yoneda, K.; Morikawa, O.; Konishi, H. *Chem. Lett.* **2000**, 798. (e) Hino, K.; Furukawa, K.; Nagai, Y.; Uno, H. *Chem. Pharm. Bull.* **1980**, *28*, 2618. (f) Hino, K.; Kawashima, K.; Oka, M.; Nagai, Y.; Uno, H.; Matsumoto, J. *Chem. Pharm. Bull.* **1989**, *37*, 110. (g) Ferrer, P.; Avendano, C.; Soellhuber, M. *Liebigs Ann. Chem.* **1995**, 1895. (h) Terpko, M. O.; Heck, R. F. *J. Am. Chem. Soc.* **1979**, *101*, 5281. (i) Kaupp, G.; Gründken, E.; Matthies, D. *Chem. Ber.* **1986**, *119*, 3109. (j) Kano, S.; Ozaki, T.; Hibino, S. *Heterocycles* **1979**, *12*, 489.

Table 3. Formation of 2-Quinolinone Derivatives



19 R = F; **22** R = OMe; **20** R = Br; **23** R = NO_2; **21** R = Me

24 R = F; **26** R = Me; **25** R = Br; **27** R = OMe

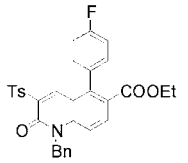
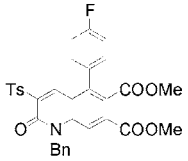
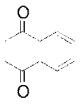
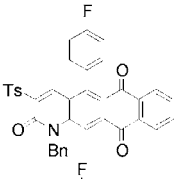
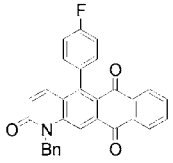
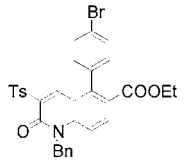
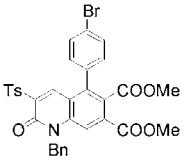
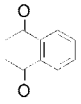
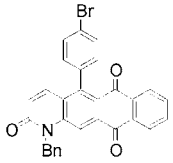
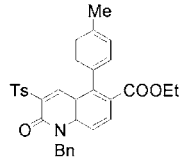
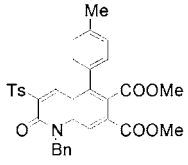
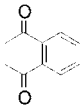
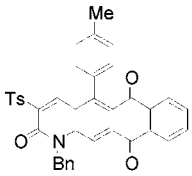
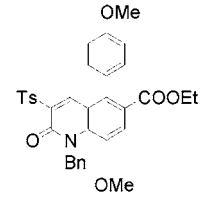
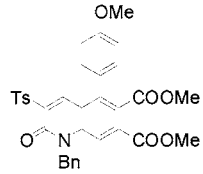
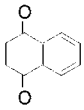
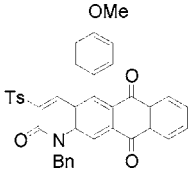
entry	diene-lactam	dienophile	2-quinolinone		yield (%)
1	**24**			**28**	41
2	**24**			**29**	60
3	**24**			**30a**	11
				**30b**	44
4	**25**			**31**	56
5	**25**			**32**	61
6	**25**			**33**	51
7	**26**			**34**	57
8	**26**			**35**	47

Table 3. Formation of 2-Quinolinone Derivatives

entry	diene-lactam	dienophile	2-quinolinone		yield (%)
9	**26**			**36**	38
10	**27**			**37**	56
11	**27**			**38**	55
12	**27**			**39**	57

Here, we wish to report a new approach to 2-quinolinones **1** in which the construction of benzene ring was at the last stage.

Recently, we developed a one-pot procedure which converted readily available glutarimide **2** to the corresponding ene lactams **3** (Scheme 1).[7] We envisioned that these results can be applied to the synthesis of *exo*-diene lactams **5**. Diels−Alder cyclization of **5** with dienophiles and then aromatization of the resulting products **6** will give 2-quinolinones **1** (Scheme 2).

We first studied the synthesis of diene lactam **8**. Sequential reaction of readily available **7**[8] with sodium hydride, methylmagnesium bromide, and then acetic anhydride furnished diene lactam **8** in 55% yield. Diene **8** is very stable and can be stored at room temperature for several months.

With diene **8** in hand, we then focused our attention on the Diels−Alder reaction of **8** with various dienophiles (Table 1). The reactions of diene **8** with alkene dienophiles provide regioselectively the corresponding bicyclic ene lactams in reasonable yield (entries 1−3).[9] Dienophiles with triple bonds similarly undergo Diels−Alder reaction (entries 4 and 5) (Table 1). In the case of ethyl propiolate, a mixture of **13a** and **13b** in a 2:1 ratio was observed. Presumably, part of **13a** was air oxidized to **13b** during the reaction. Azapolycyclic aromatic compounds have been shown in recent

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(9) Govaerts, T. C.; Vogels, I. A.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **2004**, *60*, 429.

applications to have useful optical properties.[10] Thus, we turned our attention to the Diels−Alder reactions of **8** with quinone derivatives (entries 6−8). The reactions only produced dihydroquinones **14**−**16**. Air oxidation of the Diels−Alder reaction adducts to the corresponding dihydroquinones might account for the results.

We next focused our attention on the aromatization of the Diels−Alder reaction products. Treatment of bicyclic ene lactam **12** with NBS and sodium methoxide successfully afforded 2-quinolinone derivative **17a** in 70% yield. Following a similar procedure, the mixture of **13a** and **13b** was converted to **17b**. Ene lactams **15** and **16** produced the corresponding 3-tosyl-2-quinolinones **17c** and **17d**, respectively (Table 2). Alternatively, treatment of **15** with sodium hydride and methyl iodide produced **18** (Scheme 3).

Having successfully obtained 2-quinolinones **17a**−**d** and **18**, we then examined the scope of the new approach. Following the procedures in Table 1, a series of diene lactams **24**−**27** were prepared and subjected to the Diels−Alder reaction and aromatization process. The results are shown in Table 3. Attempts to prepare imide **23** were unsuccessful.

The diene lactams which contained aromatic backbones furnished the corresponding 2-quinolinones in reasonable yield. The reaction of diene **24** with 1,4-naphthoquinone gave a mixture of **30a** and **30b** in a 1:4 ratio (entry 3). Nevertheless, diene lactam **24** afforded 2-quinolinone **33** as the sole product (entry 6). We have no clear reason for the results.

Attempts to extend this approach to alkylidene substrates **40a** and **40b** failed, presumably due to the unstability of this type of diene lactams during Diels−Alder reaction (Scheme 4).

In conclusion, we provided a new approach to 2-quinolinone derivatives which contain an aryl and electron-withdrawing groups at the benzene ring. The application of these results to the synthesis of tetracene and pentacene analogues is currently underway in our laboratory. Their optical properties will also be examined.

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Supporting Information Available: ^{1}H and ^{13}C NMR data for all new compounds and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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