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# Conjugate Additions of *o*-Iodoanilines and Methyl Anthranilates to Acetylenic Sulfones. A New Route to Quinolones Including First Syntheses of Two Alkaloids from the Medicinal Herb *Ruta chalepensis*

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A novel synthesis of 2-substituted 4-quinolones was developed on the basis of the conjugate additions of appropriately ortho-substituted anilines to acetylenic sulfones followed by intramolecular acylation of the corresponding sulfone-stabilized anions. Conjugate additions of variously substituted anilines to alkyl-substituted acetylenic sulfones generally proceeded slowly and in poor yield, especially when the aniline contained an electron-withdrawing substituent such as an ester group. In some cases, the reactions were enhanced by the presence of DMAP and the use of an excess of the sulfone in aqueous DMF. *N*-Formylanilines proved superior to free anilines. The products were either vinyl or allyl sulfones, depending on the conditions and the structure of the reactants. The acetylenic sulfone exists in equilibrium with its allenic and propargylic isomers under base-catalyzed conditions. Therefore, any of the three unsaturated sulfones can serve as the starting material for the conjugate additions. *o*-Iodoanilines proved superior to methyl anthranilate derivatives and underwent conjugate additions smoothly. The products were subjected to palladium-catalyzed carbonylation in methanol, and the resulting methyl esters were cyclized by treatment with strong bases such as LiHMDS or LiTMP, followed by reductive desulfonylation with aluminum amalgam. The resulting 2-substituted 4-quinolones included the naturally occurring medicinal compounds **1** and **2** and the *O*-methyl derivative **3**.

## Introduction

Unsaturated sulfones have proven useful in a variety of synthetic applications.[1,2] For example, the electron-withdrawing sulfone group activates adjacent double and triple bonds toward conjugate additions and cycloadditions.[2] The resulting products are saturated or vinyl sulfones, respectively, where deprotonation of the α- or γ-position is facilitated by stabilization of the corresponding anion by the sulfone group.[3] The anions in turn react with electrophiles, thereby permitting the introduction of alkyl groups or other substituents. Finally, upon completion of the desired sequence of transformations, the sulfone group can be removed reductively, oxidatively, or by substitution with certain types of organometallic reagents.[4]

During the past few years, we have developed a cyclization protocol based on the sequential application of the above processes. Thus, conjugate additions of amines containing chloroalkyl or ester substituents to acetylenic sulfones, followed by intramolecular alkylation or acylation, lead to a diverse range of nitrogen heterocycles (for some examples, see Scheme 1). The required acetylenic sulfones are readily available by the free-radical selenosulfonation[5] of the parent acetylenes, followed by selenoxide elimination or by other methods.[2a] Further functional group transformations of the adducts, ultimately including desulfonylation, provide access to the final products. To date, these have encompassed variously substituted piperidines, pyrrolizidines, indolizidines, and quinolizidines,[6] including the dendrobatid alkaloids (−)-pumiliotoxin C[7] and indolizidines (−)-167B, (−)-209D, (−)-209B, and (−)-207A,[6b] as well as the quinolizidine alkaloid (−)-lasubine II.[8]

Despite the success of this method with both primary and secondary alkylamines, its practical extension to

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(1) For general reviews of sulfone chemistry, see: (a) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993. (b) Patai, S.; Rappoport, Z., Stirling, C. J. M., Eds. *The Chemistry of Sulphones and Sulphoxides*; Wiley: Chichester, 1988.

(2) For reviews of unsaturated sulfones, see the following references. (a) Acetylenic and allenic sulfones: Back, T. G. *Tetrahedron* **2001**, *57*, 5263. (b) Vinyl sulfones: Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951. (c) Dienyl sulfones: Bäckvall, J. E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291.

(3) Block, E. *Reactions of Organosulfur Compounds*; Academic Press: New York, 1978; Chapter 2.

(4) Nájera, C.; Yus, M. *Tetrahedron* **1999**, 55, 10547.

(5) (a) Back, T. G.; Collins, S.; Kerr, R. G. *J. Org. Chem.*, **1983**, *48*, 3077. For a review of selenosulfonation, see: (b) Back, T. G. In *Organoselenium Chemistry − A Practical Approach*; Back, T. G., Ed.; Oxford University Press: Oxford, 1999; Chapter 9, pp 176−178.

(6) (a) Back, T. G.; Nakajima, K. *Org. Lett.* **1999**, *1*, 261. (b) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543.

(7) Back, T. G.; Nakajima, K. *J. Org. Chem.* **1998**, *63*, 6566.

(8) Back, T. G.; Hamilton, M. D. *Org. Lett.* **2002**, *4*, 1779.

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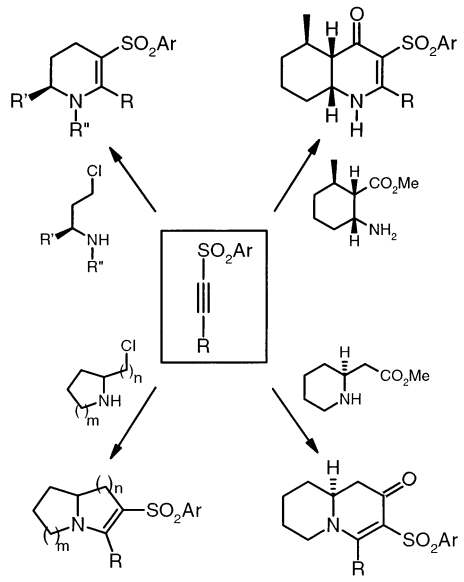
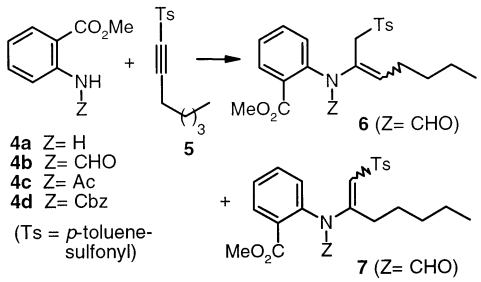
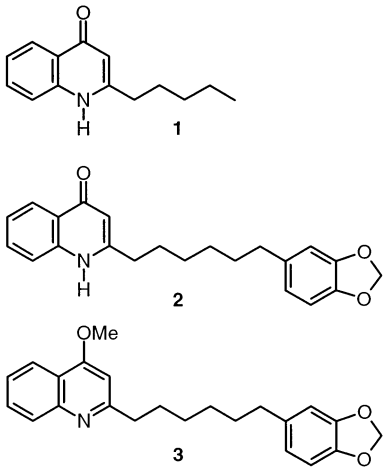
**SCHEME 1**



anilines appeared uncertain because of their considerably lower nucleophilicity. Indeed, while several detailed earlier studies of the conjugate additions of alkylamines to acetylenic sulfones have appeared,[1,2a,9] there are very few known examples of such additions using aniline derivatives.[9a,f] We now report a more detailed investigation of the conjugate additions of appropriately ortho-functionalized anilines to acetylenic sulfones and the cyclization of the products to the corresponding quinolones.[10] Members of the latter class of compounds often manifest interesting biological and medicinal properties.[11] Among the quinolones that we prepared are three natural products. Quinolone **1** was isolated from a marine pseudomonad[12a] and possesses antibiotic and other[12] biological activity. Several earlier syntheses of **1** have been reported.[12,13] We also include the first syntheses of alkaloids **2** and **3**,[14] which were recently isolated from the roots of *Ruta chalepensis*, a perennial herb collected from the northern Saudi desert, which is used in folk medicine as, inter alia, an antirheumatic and antispasmodic agent.[15]

**SCHEME 2**




## Results and Discussion

**Conjugate Additions of Methyl Anthranilates to Acetylenic Sulfone 5.** Anthranilate esters are appropriately functionalized for ring closure via intramolecular acylation, providing that the initial conjugate addition can be accomplished. We therefore investigated the addition of methyl anthranilates **4** to the representative acetylenic sulfone **5** under various conditions, as shown in Scheme 2 and Table 1. Methyl anthranilate (**4a**) and its amide and carbamate derivatives **4c** and **4d** failed to react cleanly with several acetylenic sulfones under a variety of conditions. However, greater success was realized with the similar reactions of the *N*-formyl derivative **4b** with **5** in the presence of suitable bases to generate the corresponding anion. Typically, the anthranilate and acetylenic sulfone were allowed to react in DMF−water (10:1) in the presence of potassium carbonate at room temperature. Under these conditions, **4b** afforded the corresponding conjugate addition product in

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(10) For preparations of quinolones from *o*-iodoanilines or methyl anthranilates and other types of acetylenes or allenes, see: (a) Torii, S.; Okumoto, H.; Xu, L. H. *Tetrahedron Lett.* **1991**, *32*, 237. (b) Kalinin, V. N.; Shostakovsky, M. V.; Ponomaryov, A. B. *Tetrahedron Lett.* **1992**, *33*, 373. (c) Torii, S.; Okumoto, H.; Xu, L. H.; Sadakane, M.; Shostakovsky, M. V.; Ponomaryov, A. B.; Kalinin, V. N. *Tetrahedron* **1993**, *49*, 6773. (d) Biere, H.; Seelen, W. *Liebigs Ann. Chem.* **1976**, 1972. (e) Tamura, Y.; Tsugoshi, T.; Mohri, S.; Kita, Y. *J. Org. Chem.* **1985**, *50*, 1542. (f) Doad, G. J. S.; Jordis, U.; Rudolf, M.; Sauter, F.; Scheinmann, F. *J. Chem. Res., Synop.* **1986**, 410.

(11) For selected reviews of quinolines, quinolones, and related compounds, see: (a) Openshaw, H. T. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, pp 223−267. (b) Grundon, M. F. In *The Alkaloids*; Manske, R. H. F., Rodrigo, R., Eds.; Academic Press: New York, 1979; Vol. 17, pp 105−198. (c) Grundon, M. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1988; Volume 32, pp 341−439. (d) Radl, S.; Bouzard, D. *Heterocycles* **1992**, *34*, 2143. (e) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 543 and earlier reviews by this author cited therein.

(12) (a) Wratten, S. J.; Wolfe, M. S.; Andersen, R. J.; Faulkner, D. J. *Antimicrob. Agents Chemother.* **1977**, *11*, 411. (b) Moon, S.-S.; Kang, P. M.; Yoon, K. S.; Yun, S.-J.; Park, B. B. *Bull. Korean Chem. Soc.* **1995**, *16*, 1128; via *Chem. Abstr.* **1996**, *124*, 86655f. (c) Tang, Y.; Wu, K.; Feng, X.; Huang, L. *Yaoxue Xuebao* **1998**, *33*, 121; *Chem. Abstr.* **1998**, *129*, 245022u. (d) Reil, E.; Höfle, G.; Draber, W.; Oettmeier, W. *Biochim. Biophys. Acta* **1997**, *1318*, 291. (e) Reil, E.; Höfle, G.; Draber, W.; Oettmeier, W. *Biochim. Biophys. Acta* **2001**, *1506*, 127.

(13) (a) Chong, R. J.; Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1986**, *27*, 5323. (b) Thomsen, I.; Torssell, K. B. G. *Acta Chem. Scand. B* **1988**, *42*, 309. (c) Beifuss, U.; Ledderhose, S. *Synlett* **1997**, 313. (d) Buu-Hoi, N. P.; Royer, R.; Xuong, N. D.; Jacquignon, P. *J. Org. Chem.* **1953**, *18*, 1209.

(14) Preliminary communication: Back, T. G.; Wulff, J. E. *J. Chem. Soc., Chem. Commun.* **2002**, 1710.

(15) El Sayed, K.; Al-Said, M. S.; El-Feraly, F. S.; Ross, S. A. *J. Nat. Prod.* **2000**, *63*, 995.

**TABLE 1. Addition of Methyl Anthranilate 4b to Sulfones 5, 8, and 9**[a]

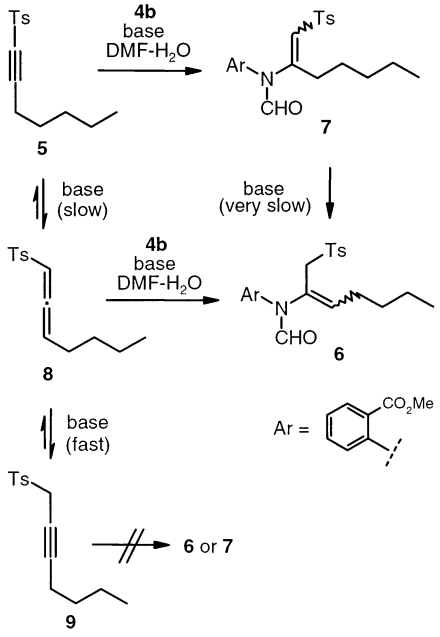
| entry | sulfone (equiv) | base | reaction time | combined yield (%) and ratio of **6**/**7** |
|---|---|---|---|---|
| 1 | **5** (1.0) | $K_2CO_3$ | 4 d | 20 (81:19) |
| 2 | **5** (2.0) | $K_2CO_3$−DMAP | 2 h | 57 (100:0) |
| 3 | **8** (2.0) | $K_2CO_3$ | 4 d | 18 (100:0) |
| 4 | **8** (2.0) | $K_2CO_3$−DMAP | 2 h | 60 (100:0) |
| 5 | **9** (2.0) | $K_2CO_3$−DMAP | 1 d | 51 (100:0) |

[a] All reactions were performed at room temperature in DMF-water (10:1).

low yield after 4 days, isolated as a chromatographically separable mixture of allyl and vinyl sulfones **6** and **7** in a ratio of 81:19 (Table 1, entry 1). Each product was in turn obtained as a mixture of unseparated geometrical isomers. Large amounts of unreacted **4b** remained, along with decomposition products of **5**. A slightly higher yield of 27% of **6** and none of isomer **7** was obtained after 25 days, but no improvement was observed at higher temperatures, with the use of other bases such as cesium carbonate or triethylamine, or in other solvents (aqueous methanol, ethanol, acetonitrile or HMPA, or anhydrous DMF, THF, or acetonitrile). We observed that the addition of DMAP[16] to the reaction mixture improved the rate and yield significantly but also caused more rapid decomposition of the acetylenic sulfone **5**. Thus, an excess of the latter was employed for optimum results (entry 2). These experiments indicate that anilines containing an electron-withdrawing ester substituent react too slowly with a typical acetylenic sulfone to be of practical value. However, the enhancement of the reaction rate and yield by DMAP (entry 2) suggest a means to partly overcome the low reactivity of such systems.

It is noteworthy that in Table 1 the allyl sulfone **6** was in each case the chief or sole product formed, whereas the isomeric vinyl sulfone **7** is the expected product of direct conjugate addition to acetylenic sulfone **5**. It has been reported that allyl sulfones can be produced from their vinyl counterparts by base-catalyzed isomerization.[17] Thus, the predominance of **6** could be the result of initial conjugate addition to afford **7**, followed by isomerization to **6**. On the other hand, it is also known that the equilibration of acetylenic, allenic, and propargylic sulfones can be promoted by bases.[2a,18] An alternative possible explanation for the dominant formation of **6** is therefore the isomerization of acetylenic sulfone **5** to its allenic counterpart **8** prior to conjugate addition. These pathways are indicated in Scheme 3. Several control experiments were conducted to distinguish between these possibilities. First, when **7** was subjected to the conditions of entries 1 or 2 in Table 1, it was found

**SCHEME 3**




to isomerize to **6** too slowly to account for the dominant or exclusive formation of **6** in these entries. Moreover, an authentic sample of the allenic sulfone **8** was prepared by selenosulfonation, base-catalyzed isomerization, and selenoxide elimination[17a] and was subjected to the same conditions. In this case, the allylic sulfone **6** was produced in 18% and 60% yield in the absence or presence of DMAP after 4 days and 2 h, respectively (entries 3 and 4). These results are similar to those that were obtained with acetylenic sulfone **5** (entries 1 and 2) and are therefore consistent with the formation of **6** via prototropic isomerization of **5** to **8** prior to the conjugate addition of **4b**. We also observed no detectable isomerization of **6** to **7**, even after prolonged reaction times. The formation of the minor product **7** in entry 1 is therefore attributed to the direct addition of **4b** to acetylenic sulfone **5**.

In the absence of DMAP, the propargylic sulfone **9** proved to be a major byproduct. When each of the triad of isomeric sulfones **5**, **8**, and **9** was treated independently with potassium carbonate in aqueous DMF, the sole product in each case was **9**, indicating that it is the thermodynamically favored isomer. Furthermore, the formation of **9** from acetylenic sulfone **5** required several days to go to completion, whereas that from allenic sulfone **8** was complete in 15 min. Since **8** is presumably an intermediate in the overall conversion of **5** to **9**, we conclude that the isomerization of **5** to **8** is relatively slow compared to the subsequent isomerization of **8** to **9** (Scheme 3). Unlike **5** and **8**, propargylic sulfone **9** contains an unactivated triple bond and therefore cannot undergo direct conjugate addition. To test whether it can return to the manifold in Scheme 3 by reisomerization back to the allenic isomer **8**, we allowed **9** to react with **4b** under the usual conditions and found that it afforded a comparable yield of adduct **6** (entry 5) as had been obtained directly from **8** (entry 4). Thus, while the propargylic isomer **9** is the most stable sulfone, all three isomers are in equilibrium under base-catalyzed conditions and each one can be employed as the starting material for the conjugate additions. The precise role of

(16) For a review of nucleophilic catalysis with DMAP and related compounds, see: Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.

(17) For examples, see: (a) Back, T. G.; Krishna, M. V.; Muralidharan, K. R. *J. Org. Chem.* **1989**, *54*, 4146. (b) Block, E.; Aslam, M. *J. Am. Chem. Soc.* **1983**, *105*, 6164. (c) Block, E.; Eswarakrishnan, V.; Gebreyes, K. *Tetrahedron Lett.* **1984**, *25*, 5469. (d) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 3279. (e) Baldwin, J. E.; Adlington, R. M.; Ichikawa, Y.; Kneale, C. J. *J. Chem. Soc., Chem. Commun.* **1988**, 702. (f) Sváta, V.; Procházka, M.; Bakos, V. *Collect. Czech. Chem. Commun.* **1978**, *43*, 2619. (g) Broaddus, C. D. *J. Am. Chem. Soc.* **1966**, *88*, 3863. (h) Broaddus, C. D. *J. Am. Chem. Soc.* **1968**, *90*, 5504.

(18) (a) Stirling, C. J. M. *J. Chem. Soc.* **1964**, 5856. (b) Mackle, H.; Steele, W. V. *Trans. Faraday Soc.* **1969**, 65, 2073. (c) Smith, G.; Stirling, C. J. M. *J. Chem. Soc. C* **1971**, 1530. (d) Braverman, S.; Mechoulam, H. *Tetrahedron* **1974**, *30*, 3883.

**CHART 1**

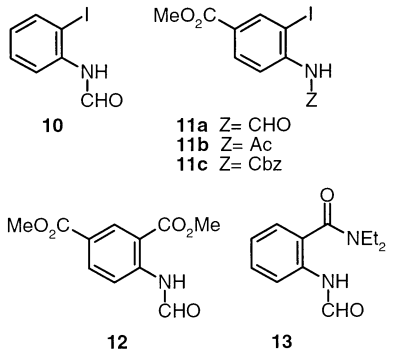
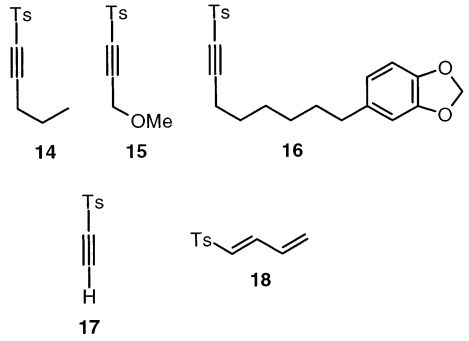



**CHART 2**



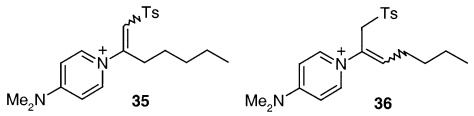

DMAP in these processes is not entirely clear. However, the observation that the addition of **4b** to authentic allenic sulfone **8** in the absence of DMAP (entry 3) proceeded slowly and afforded only 18% of **6** after 4 days, compared to 60% in 2 h in the presence of DMAP (entry 4), indicates that DMAP is implicated in the conjugate addition itself and does not merely serve to promote the isomerization of **5** to **8**.[19]

**Conjugate Additions of Other Anilines to Unsaturated Sulfones.** A series of anilines **10**−**13** (Chart 1) was prepared by routine methods (see the Experimental Section and Supporting Information). The other unsaturated sulfones that were studied are shown in Chart 2. Acetylenic sulfones **14**[7] and **15**[20] were prepared by selenosulfonation[5] and selenoxide elimination of the parent acetylenes. The synthesis of compound **16** was achieved as indicated in our preliminary communication,[14] and details are provided in the Supporting Information. We also wished to investigate conjugate additions to the unsubstituted acetylenic sulfone **17**[21] and the dienyl sulfone **18**,[22] which were both available by literature methods. Apart from **8** (vide supra), we did not investigate allenic sulfones, since they are less convenient to prepare and, in some cases, less stable than their acetylenic isomers. However, it should be kept in mind that, as in the case of **5** and **8**, other allenic sulfones may be formed in situ from their acetylenic counterparts and may comprise the actual electrophiles under the conditions of the conjugate additions.

Conjugate additions of anilines to acetylenic sulfones **5** and **14**−**16** are shown in Table 2. The optimized addition of **4b** to **5** (Table 1, entry 2) is included in Table 2 (entry 1) for comparison. As expected, higher yields of addition products were generally obtained when the less deactivated *o*-iodoanilines **10**, **11a**, and **11b** were employed instead of *o*-esters **4b** or **12** or *o*-amide **13** (i.e., compare entry 2 with 1, entry 4 with 3, and entry 9 with 7 or 8 in Table 2). Furthermore, the *o*-iodoanilines typically produced excellent yields of adducts even in the absence of DMAP (entries 2, 4, and 5) and even when an ester substituent was present in the para position (entries 4 and 5). We also observed that the methoxymethyl-substituted acetylenic sulfone **15** displayed remarkably high reactivity compared to the alkyl-substituted analogues **5**, **14**, and **16**. Thus, **15** afforded an excellent yield of the corresponding adduct **23**, even with the doubly deactivated aniline **12** (entry 6), whereas the alkyl-substituted acetylenic sulfone **14** produced a much poorer yield of adduct **20** with the same aniline (entry 3). However, since **15** decomposed more rapidly than the other acetylenic sulfones under similar reaction conditions, a 2-fold excess was employed to compensate. Acetylenic sulfone **15** did not isomerize to the corresponding allenic sulfone at an appreciable rate in DMF−water−potassium carbonate. This observation, together with the exclusive formation of the vinyl sulfones **22B** and **23B** (entries 5 and 6), suggests that the unusually high reactivity is an intrinsic property of **15** itself and is not due to its facile isomerization to a more reactive allenic isomer. In contrast to the failure of the acetanilide **4c** to react with **5**, the *o*-iodoacetanilide **11b** reacted smoothly with **15** (Table 2, entry 5). In entries 1, 2, 4, and 7−9, products **6**, **19**, **21**, and **24**−**26**, respectively, were formed exclusively as the allyl sulfone isomers (structures **A** in Table 2). Product **20** (entry 3) was isolated as a mixture of allyl and vinyl sulfone isomers (structures **A** and **B**, respectively) in the ratio of 70:30. Since structural assignments (allyl vs vinyl sulfone) of the products **22** and **23** of entries 5 and 6 were equivocal when based only on their NMR spectra, an X-ray structure of the *Z*-isomer of **22** was obtained (see the Supporting Information), thus confirming that it was the vinyl sulfone (structure **B**). Product **23** had an NMR spectrum similar to that of **22** and was also assigned the vinyl sulfone structure **B** by analogy. Each product in Table 2, as in the case of **6** and **7** in Table 1, was obtained as an unseparated mixture of geometrical isomers.

The conjugate additions of anilines **11a** and **11c** to the unsubstituted acetylenic sulfone **17** and the dienyl sulfone **18** were also investigated, and the results are shown

(19) While one could rationalize the formation of **7** from **5** and **4b** via an addition−elimination reaction of the corresponding DMAP adduct **35** with the conjugate base of **4b**, the isomeric adduct **36**, which would be obtained from allene **8** and DMAP, and which would be expected to lead to **6** after a similar sequence, does not contain an activated double bond for such an addition−elimination. Thus, DMAP may play a more complex role in these additions.

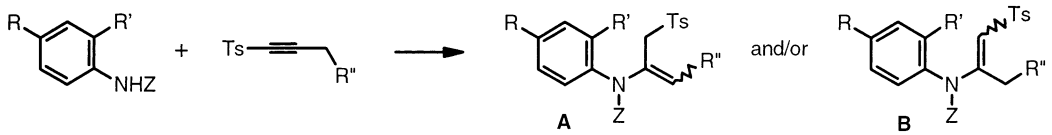



(20) This compound was reported by: Miura, T.; Kobayashi, M. *J. Chem. Soc., Chem. Commun.* **1982**, 438. We obtained it similarly, but using photochemical selenosulfonation (see ref 5b) and *m*-CPBA in the selenoxide elimination step.

(21) (a) Bhattacharya, S. N.; Josiah, B. M.; Walton, D. R. M. *Organomet. Chem. Synth.* **1970/1971**, *1*, 145. (b) Waykole, L.; Paquette, L. A. *Org. Synth.* **1989**, 67, 149. (c) Chen, Z.; Trudell, M. L. *Synth. Commun.* **1994**, *24*, 3149.

(22) Barluenga, J.; Martinez-Gallo, J. M.; Nájera, C.; Fañanás, F. J.; Yus, M.; *J. Chem. Soc., Perkin Trans. 1* **1987**, 2605.

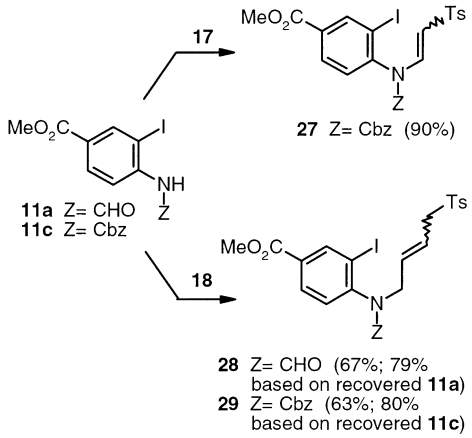
**TABLE 2. Addition of Anilines to Acetylenic Sulfones**[a]




| entry | aniline | R | R′ | Z | sulfone (equiv) | R″ | reaction time | product, yield (%), and (ratio of A/B) |
|---|---|---|---|---|---|---|---|---|
| 1 | **4b** | H | $CO_2Me$ | CHO | **5** (2.0) | *n*-Bu | 2 h[b] | **6**, 57 (100:0) |
| 2 | **10** | H | I | CHO | **5** (1.0) | *n*-Bu | 8 d[c] | **19**, 81 (100:0) |
| 3 | **12** | $CO_2Me$ | $CO_2Me$ | CHO | **14** (1.25) | Et | 4 d[c] | **20**, 27 (70:30) |
| 4 | **11a** | $CO_2Me$ | I | CHO | **14** (1.25) | Et | 17 h[c] | **21**, 82 (100:0) |
| 5 | **11b** | $CO_2Me$ | I | Ac | **15** (2.0) | OMe | 10 h[c] | **22**, 89 (0:100) |
| 6 | **12** | $CO_2Me$ | $CO_2Me$ | CHO | **15** (2.0) | OMe | 16 h[c] | **23**, 96 (0:100) |
| 7 | **4b** | H | $CO_2Me$ | CHO | **16** (1.0) | $Ar(CH_2)_5$[d] | 15 h[b] | **24**, 26 (100:0) |
| 8 | **13** | H | $CONEt_2$ | CHO | **16** (1.0) | $Ar(CH_2)_5$[d] | 2 d[b] | **25**, 66 (100:0) |
| 9 | **10** | H | I | CHO | **16** (1.0) | $Ar(CH_2)_5$[d] | 2 d[b] | **26**, 79 (100:0) |

[a] All reactions were performed in 10:1 DMF−$H_2O$ containing $K_2CO_3$. [b] Conducted with 1 equiv of DMAP. [c] Conducted without DMAP. [d] Ar = 3,4-(methylenedioxy)phenyl.

**SCHEME 4**




in Scheme 4. Acetylene **17** reacted smoothly with the *N*-Cbz aniline **11c** in the absence of DMAP. In contrast to the earlier experiment, where the *N*-Cbz analogue **4d** failed to react with acetylenic sulfone **5**, while the *N*-formyl analogue **4b** gave slightly better results (entry 1 in Table 1), here the *N*-formyl analogue **11a** gave very poor yields in attempted additions to **17**. On the other hand, **11a** and **11c** produced comparable results with the dienyl sulfone **18**. The products **27**−**29** are potential substrates for radical cyclization reactions.[23]

These experiments show that *o*-iodoanilines provide enhanced reactivity and afford improved yields compared to anthranilate esters in conjugate additions, even in the absence of DMAP. Moreover, the use of more reactive unsaturated sulfones (e.g., **15**), compared with alkyl-substituted derivatives (e.g., **5**), permit efficient conjugate additions even with doubly deactivated anilines such as **12**.

**Carbonylations and Cyclizations.** The *o*-iodo adducts **19**, **21**, and **26** were converted into the corresponding esters **6**, **20**, and **24**, respectively, in excellent yield by palladium-catalyzed carbonylation in methanol at 27 atm (400 psi).[24] Adduct **27** underwent similar carbonylation to afford **33**. Thus, the carbonylation of *o*-iodo conjugate addition products such as **19**, **21**, and **26** smoothly circumvents the difficulties arising from the direct additions of electron-deficient anthranilates to acetylenic sulfones. Esters **6**, **20**, and **24** were then treated with excess LiHMDS in THF and the resulting sulfone-stabilized anions underwent intramolecular acylation,[25] affording the corresponding quinolones **30**−**32**, respectively (Scheme 5). Diester **23** reacted more slowly but was cyclized and simultaneously deformylated quantitatively with LiTMP in THF to **34**. On the other hand, diethylamide **25** failed to cyclize under a variety of conditions, while the cyclization of **33**, which requires the formation of a vinyl anion (as opposed to an allyl anion), was also unsuccessful. *N*-Formyl products **30**−**32** were formed with exocyclic double bonds as single geometrical isomers, while the deprotected **34** was obtained as the enaminone tautomer. Quinolone **34** serves as a potential advanced intermediate for the synthesis of the antiviral agent virantmycin.[26]

**Synthesis of Alkaloids 1−3.** The synthesis of **1**−**3** from quinolones **30** and **32** was completed as shown in Scheme 6. Thus, **30** was subjected to reductive desulfonylation with aluminum amalgam,[27] resulting in simultaneous deformylation and tautomerization to the corresponding enaminone **1**, isolated in 68% yield, thus

(23) For some reviews of radical cyclization, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon*−*Carbon Bonds*; Pergamon Press: Oxford, 1986; Chapter 4. (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (c) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 4.2. (d) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992, Chapter 7. (e) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (f) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React. (N.Y.)* **1996**, *48*, 301. (g) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York, 1996. (h) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.

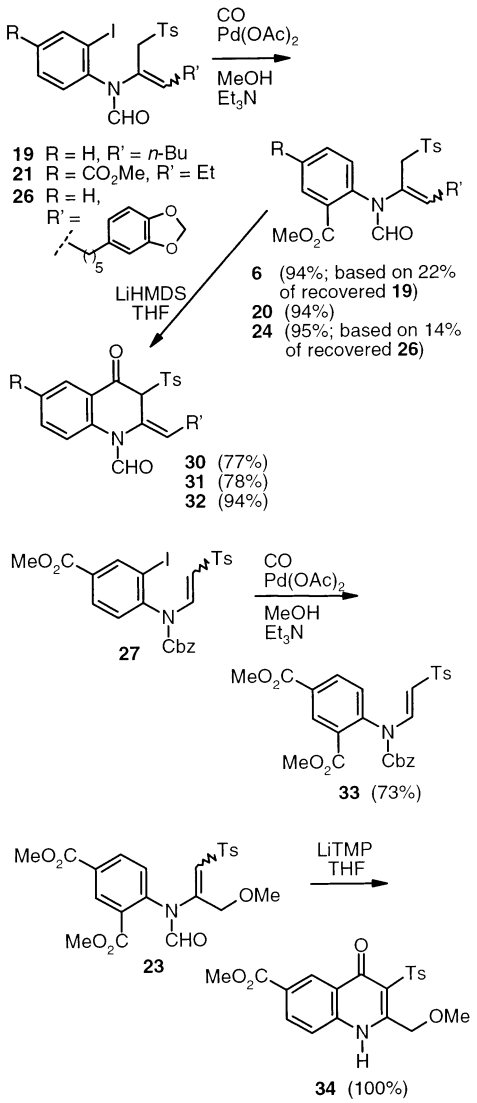
(24) Tsuji, J. *Palladium Reagents and Catalysts*, Wiley: Chichester, 1995; pp 188−209.

(25) For other examples of intramolecular acylations of sulfone-stabilized anions, see: (a) Grimm, E. L.; Levac, S.; Coutu, M. L. *Tetrahedron Lett.* **1994**, *35*, 5369. (b) Grimm, E. L.; Coutu, M. L. Trimble, L. A. *Tetrahedron Lett.* **1993**, *34*, 7017.

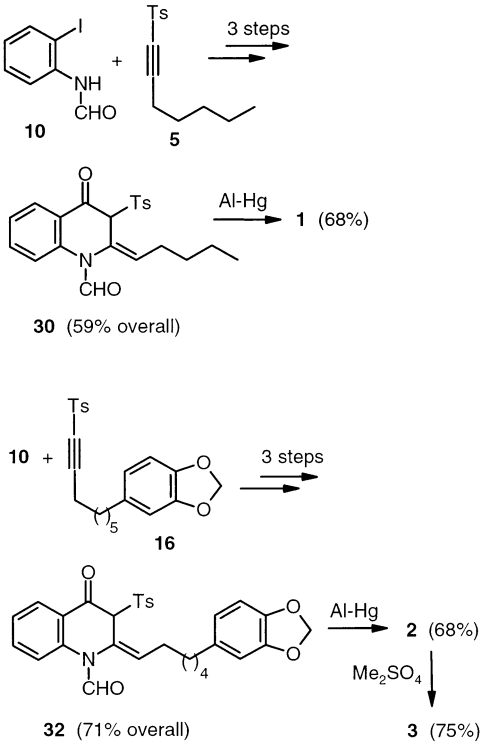
(26) (a) Omura, S.; Nakagawa, A.; Hashimoto, H.; Oiwa, R.; Iwai, Y.; Hirano, A.; Shibukawa, N.; Kojima, Y. *J. Antibiot.* **1980**, *33*, 1395. (b) Nakagawa, A.; Iwai, Y.; Hashimoto, H.; Miyazaki, N.; Oiwa, R.; Takahashi, Y.; Hirano, A.; Shibukawa, N.; Kojima, Y.; Omura, S. *J. Antibiot.* **1981**, *34*, 1408.

(27) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1964**, *86*, 1639.

**SCHEME 5**




**SCHEME 6**




providing **1** from aniline **10** and acetylenic sulfone **5** in an overall yield of 40%. Similarly, desulfonylation, deformylation, and tautomerization of **32** afforded the alkaloid **2**, obtained in 48% overall yield from aniline **10** and acetylenic sulfone **16**. *O*-Methylation and aromatization of **2** furnished the remaining alkaloid **3** in 75% yield. This approach therefore provides a concise and efficient route to these biologically interesting alkaloids.

The $^1$H and $^{13}$C NMR spectra of **1**−**3** were in generally close agreement with the reported spectra.[12a,15] However, in the $^1$H NMR spectrum of **2**, we noted a significant concentration dependence, particularly of the chemical shifts of the signals at $\delta$ 7.73, 7.58, and 5.87, attributed to H-8, H-7, and H-3, respectively.[15] These chemical shifts were also sensitive to the presence or absence of trace acids. Similar effects were observed with quinolone **1**. The concentration and pH dependence may be the result of changes in the equilibrium between the enaminone and corresponding pyridinol tautomers or to changes in intermolecular hydrogen bonding, leading to some uncertainty about the exact structures of alkaloids **1** and **2**. We note that the pyridinol structure was assigned to the natural product **1**,[12a] whereas **2** was reported as the corresponding enaminone.[15] Since **1** is a crystalline compound, we obtained its X-ray structure in order to determine the dominant tautomer in the solid state. The ORTEP diagram of **1** clearly confirms the presence of the enaminone tautomer. Interestingly, **1** exists as a dimeric species in the solid state, in which the N−H moiety of one molecule is hydrogen-bonded to the carbonyl oxygen atom of the other molecule (see the Supporting Information).

## Summary and Conclusions

A new methodology for the synthesis of quinolones was developed on the basis of the conjugate additions of suitably ortho-substituted anilines to acetylenic sulfones followed by intramolecular acylations of the corresponding sulfone-stabilized anions. The conjugate additions of various anthranilate esters to alkyl-substituted acetylenic sulfones, such as **5**, proceed slowly and in poor yield. The reactions were enhanced by the use of *N*-formyl anthranilates and by the addition of DMAP with the concomitant use of excess sulfone. More reactive acetylenic sulfones such as **15** undergo conjugate addition of anthranilates smoothly even without DMAP. Acetylenic, allenic, and propargylic sulfones **5**, **8**, and **9** were found to equilibrate under basic conditions, with **9** being the most stable isomer. However, even the latter, which contains an unactivated triple bond, can be employed in conjugate additions by its in situ isomerization to allenic sulfone **8**. In at least some cases, it appears that the additions proceed via isomerization of the acetylenic sulfone to the corresponding allene derivative prior to addition of the aniline. A more generally successful alternative to the use of deactivated anilines such as anthranilates was also developed. It employs the more nucleophilic *o*-iodoaniline analogues, which undergo conjugate additions to acetylenic sulfones smoothly, followed by palladium-catalyzed carbonylation to introduce the

*o*-ester moiety required for cyclization to the desired quinolones. The cyclizations were effected in excellent yield via deprotonation and intramolecular acylation of the conjugate addition products. When used in conjunction with reductive desulfonylation, this protocol was successfully applied to the first syntheses of the biologically interesting *Ruta chalepensis* alkaloids **2** and **3** as well as to that of the previously synthesized alkaloid **1**.

## Experimental Section

**General Methods.** All reagents, unless otherwise noted, were obtained from commercial sources and purified by standard methods as necessary. Anilines **4b**,[28] **4d**,[29] **10**,[30] **11c**,[31] and **13**,[32] unsaturated sulfones **5**,[6b] **14**,[7] **15**,[20] **17**,[21] and **18**,[22] as well as *Se*-phenyl *p*-tolueneselenosulfonate[33] and methyl 3-iodo-4-aminobenzoate[34] were prepared by literature procedures. The preparations of new anilines **11a** and **12**, the known aniline **11b**,[35] and the novel acetylenic sulfone **16** are described in the Supporting Information. Chromatography refers to flash chromatography on silica gel (230−400 mesh). NMR spectra were recorded in deuteriochloroform unless otherwise indicated.

**1-(*p*-Toluenesulfonyl)-1,2-heptadiene (8).** 1-Heptyne (1.05 mL, 8.00 mmol) and *Se*-phenyl *p*-tolueneselenosulfonate (2.50 g, 8.03 mmol) were dissolved in 20 mL of chloroform and irradiated for 2 h in a Rayonet reactor equipped with six 300 nm lamps. The solvent was evaporated, and the residue was redissolved in 20 mL of THF. Potassium *tert*-butoxide (1.35 g, 12.0 mmol) was added, and the mixture was stirred for 6 h at room temperature and then partitioned between ether and water. The aqueous layer was washed with ether, and the combined organic layers were dried and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 9:1−4:1) gave 1.63 g (50%) of a single geometrical isomer of the corresponding $\beta$-(phenylseleno)allyl sulfone. Purification of the other geometrical isomer was complicated by coelution with residual vinyl sulfone.

The $\beta$-(phenylseleno)allyl sulfone intermediate was dissolved in 30 mL of chloroform. *m*-CPBA (1.8 g, ca. 77% purity, 8.0 mmol) was added, and the resulting mixture was stirred for 15 min and then washed twice with 5% NaOH solution. The aqueous layers were extracted twice with chloroform to ensure that the partly water-soluble selenoxide was not lost. The combined organic layers were dried and refluxed in the presence of anhydrous $MgSO_4$ for 90 min. The mixture was filtered, and the filtrate was concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 9:1 to 4:1) gave 732 mg (73%; 37% overall from 1-heptyne) of **8** as a colorless oil: IR (film) 1953, 1596 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 7.74 (d, $J$ = 8.3 Hz, 2 H), 7.29 (d, $J$ = 8.3 Hz, 2 H), 6.14 (dt $J$ = 6.0, 3.0 Hz, 1 H), 5.79 (dt, $J$ = 6.9, 6.0 Hz, 1 H), 2.39 (s, 3 H), 2.13−2.03 (m, 2 H), 1.38−1.22 (m, 4 H), 0.84 (t, $J$ = 7.1 Hz, 3 H); $^{13}C$ NMR (100 MHz) $\delta$ 205.3, 144.2, 138.4, 129.6, 127.5, 101.2, 100.9, 30.3, 27.2, 21.8, 21.4, 13.6; MS (ESI) *m*/*z* (%) 523 (2 × $M^+$ + Na), 273 ($M^+$ + Na); HRMS calcd for $C_{14}H_{18}O_2S$ 250.1028, found 250.1039.

**1-(*p*-Toluenesulfonyl)-2-heptyne (9).**[36] A mixture of allenic sulfone **8** (105 mg, 0.419 mmol) and $K_2CO_3$ (49 mg, 0.35 mmol) in 0.5 mL of DMF−water (10:1) was stirred for 15 min. The mixture was partitioned between ether and water, the aqueous layer was washed with ether, and the combined organic fractions were dried and concentrated in vacuo. Chromatography (hexanes−ethyl acetate 6:1 to 4:1) afforded 80 mg (76%) of a 10:1 mixture of **9** and **8**. Propargyl sulfone **9**: IR (film) 2234, 1596, 1324 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 7.84 (d, $J$ = 8.4 Hz, 2 H), 7.36 (d, $J$ = 8.4 Hz, 2 H), 3.92 (t, $J$ = 2.5 Hz, 2 H), 2.46 (s, 3 H), 2.22−2.08 (m, 2 H), 1.50−1.23 (m, 4 H), 0.87 (t, $J$ = 7.0 Hz, 3 H); $^{13}C$ NMR (50 MHz) $\delta$ 145.0, 135.0, 129.5, 128.8, 88.7, 67.6, 49.1, 30.2, 21.8, 21.6, 18.4, 13.5.

**Conjugate Addition of Aniline 4b to Acetylenic Sulfone 5 (Table 1, Entry 1; Typical Procedure).** A mixture of aniline **4b** (75 mg, 0.42 mmol), $K_2CO_3$ (58 mg, 0.42 mmol), and sulfone **5** (105 mg, 0.419 mmol) in 0.5 mL of DMF−water (10:1) was stirred vigorously for 4 d at room temperature. TLC analysis then revealed the presence of a significant amount of **4b**, as well as of **9** and two new products. The mixture was partitioned between ether and water, the aqueous layer was washed with ether, and the combined organic fractions were dried and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 4:1−2:1) afforded 29 mg (16%) of **6** and 7 mg (4%) of **7**.

**Adduct 6.** NMR analysis showed the product to be a 2:1 mixture of geometrical isomers: IR (film) 1727, 1689 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 8.34 (s, major isomer) and 8.09 (s, minor isomer, total 1 H), 7.88−7.67 (m, 3 H), 7.62−7.22 (m, 5 H), 5.84 (t, $J$ = 7.6 Hz, major isomer) and 5.59 (t, $J$ = 7.6 Hz, minor isomer, total 1 H), 4.22 (br s, minor isomer) and 3.70 (br s, major isomer, total 2 H), 3.78 (s, both isomers, 3 H), 2.40 (s, both isomers, 3 H), 1.88−1.68 (m, 2 H), 1.30−1.08 (m, 4 H), 0.85−0.71 (m, 3 H); $^{13}C$ NMR (100 MHz, both isomers) $\delta$ 166.1, 166.0, 161.8, 161.7, 145.1, 144.7, 140.0, 137.3, 137.0, 136.3, 136.2, 135.6, 133.4, 132.6, 131.0, 130.9, 130.2, 129.9, 129.7, 129.5, 129.2, 128.3, 128.1, 128.0, 126.4, 126.1, 55.0, 54.5, 52.3, 52.2, 30.9, 30.7, 27.8, 27.2, 22.1, 22.0, 21.4, 13.6, 13.6; MS (EI) *m*/*z* 326 (7), 280 (7), 274 (5), 246 (100); HRMS calcd for $C_{16}H_{20}NO_3$ ($M^+$ − Ts) 274.1443, found 274.1458.

**Adduct 7.** NMR analysis showed the product to be a 4:1 mixture of geometrical isomers: IR (film) 1726, 1701 $cm^{-1}$; $^1H$ NMR (400 MHz, major isomer) $\delta$ 8.35 (s, 1 H), 7.94 (dd, $J$ = 7.7, 1.5 Hz, 1 H), 7.86 (d, $J$ = 8.3 Hz, 2 H), 7.51 (td, $J$ = 7.7, 1.6 Hz, 1 H), 7.44−7.33 (m, 3 H), 6.93 (d, $J$ = 7.8 Hz, 1 H), 6.34 (s, 1 H), 3.85 (s, 3 H), 2.46 (s, 3 H), 2.19−2.12 (m, 2 H), 1.49−1.39 (m, 2 H), 1.22−1.09 (m, 4 H), 0.80 (t, $J$ = 7.0 Hz, 3 H); signals from the minor isomer were observed at $\delta$ 8.13 (s), 6.40 (s); $^{13}C$ NMR (100 MHz, major isomer) $\delta$ 166.0, 161.5, 151.9, 144.8, 138.7, 135.6, 132.9, 131.0, 130.2, 128.2, 128.2, 127.6, 126.8, 122.5, 52.4, 34.6, 31.0, 26.9, 22.2, 21.6, 13.8; MS (EI) *m*/*z* 370 (2), 326 (4), 280 (100); HRMS calcd for $C_{16}H_{20}NO_3$ ($M^+$ − Ts) 274.1443, found 274.1440.

The other experiments listed in Table 1 were performed in a similar manner, with any changes noted in the table.

**Conjugate Additions of Other Anilines to Unsaturated Sulfones (Table 2).** These reactions were performed by the same general procedure as described above for entry 1 in Table 1. The yields of products **19**−**26**, as well as any changes to the general experimental conditions, are indicated in Table 2. The properties of the products are given below.

(28) Kobayashi, K.; Nakashima, T.; Mano, M.; Morikawa, O.; Konishi, H. *Chem. Lett.* **2001**, 602.

(29) Aniline **4d** was prepared from methyl anthranilate and benzyl chloroformate, using an identical procedure to that given in ref 31 for the similar protection of **11c**.

(30) Hays, S. J.; Caprathe, B. W.; Gilmore, J. L.; Amin, N.; Emmerling, M. R.; Michael, W.; Nadimpalli, R.; Nath, R.; Raser, K. J.; Stafford, D.; Watson, D.; Wang, K.; Jaen, J. C. *J. Med. Chem.* **1998**, *41*, 1060.

(31) Back, T. G.; Bethell, R. J.; Parvez, M.; Taylor, J. A. *J. Org. Chem.* **2001**, *66*, 8599.

(32) Anthranilic acid was converted into its acyl chloride via the procedure of: Hermecz, I.; Szilagyi, I.; Orfi, L.; Kokosi, J.; Szasz, G. *J. Heterocycl. Chem.* **1993**, *30*, 1413. Amide **13** was prepared by reacting the acyl chloride with diethylamine, then protecting with ethyl formate and sodium hydride via the procedure of ref 30.

(33) Back, T. G.; Collins, S.; Krishna, M. V. *Can. J. Chem.* **1987**, *65*, 38.

(34) Methyl 3-iodo-4-aminobenzoate was prepared by a variation of the procedure of: Hill, M. L.; Raphael, R. A. *Tetrahedron* **1990**, *46*, 4587. Slow addition of the iodine monochloride reagent to the reaction mixture afforded an improved yield of 95%.

(35) Aniline **11b** has been previously prepared by a different method, but spectroscopic data was not provided: Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307.

(36) Sulfone **9** has been previously prepared by a different method, but spectroscopic data was not provided: Ozawa, M.; Iwata, N.; Kinoshita, H.; Inomata, K. *Chem. Lett.* **1990**, 1689.

**Adduct 19 (Table 2, Entry 2).** The adduct was obtained as a pale yellow foam. NMR analysis showed the product to be the pure allyl sulfone isomer, obtained as a 2:1 mixture of geometrical isomers: IR (film) 1686 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 8.39 (s, major isomer) and 8.15 (s, minor isomer, total 1 H), 7.90−7.83 (m), 7.75 (d, $J$ = 8.3 Hz, major isomer), 7.50−7.41 (m) and 7.38−7.33 (m, total 7 H for peaks between $\delta$ 7.90 and 7.33), 7.12−7.02 (m, 1 H), 6.01 (t, $J$ = 7.6 Hz, major isomer) and 5.68 (t, $J$ = 7.6 Hz, minor isomer, total 1 H), 4.5−4.0 (br m, minor isomer) and 4.0−3.3 (br m, major isomer, total 2 H), 2.43 (s, both isomers, 3 H), 2.00−1.63 (m, 2 H), 1.33−1.11 (m, 4 H), 0.83 (t, $J$ = 7.1 Hz, major isomer), 0.77 (t, $J$ = 6.9 Hz, minor isomer, total 3 H); $^{13}C$ NMR (100 MHz, both isomers) $\delta$ 162.4, 161.9, 145.3, 144.8, 142.5, 140.7, 140.1, 138.6, 138.2, 137.1, 136.0, 136.0, 131.4, 131.1, 130.2, 130.1, 130.1, 130.0, 129.7, 129.4, 128.5, 128.2, 125.2, 124.7, 54.4, 54.1, 30.8, 30.7, 27.8, 27.1, 22.2, 22.1, 22.1, 21.5, 13.7, 13.6.; MS (EI) *m*/*z* 342 (44), 314 (41), 270 (63), 186 (93), 144 (99), 143 (100); HRMS calcd for $C_{14}H_{17}INO$ ($M^+$ − Ts) 342.0355, found 342.0376.

**Adduct 20 (Table 2, Entry 3).** The adduct was obtained as a pale yellow foam. NMR analysis showed the product to be a 7:3 mixture of the allyl and vinyl sulfone isomers, formed as 2:1 and 6:1 mixtures of geometrical isomers, respectively. Further chromatography (hexanes−ethyl acetate 4:1−2:1) afforded the pure (*E*,*Z*)-vinyl sulfone, but the allyl sulfone could not be completely separated from its vinyl counterparts.

Allyl sulfone: IR (film) 1727, 1690 $cm^{-1}$; $^1H$ NMR (400 MHz) major isomer $\delta$ 8.46 (d, $J$ = 2.0 Hz, 1 H), 8.36 (s, 1 H), 8.16 (dd, $J$ = 8.3, 2.0 Hz, 1 H), 7.74 (d, $J$ = 8.3 Hz, 2 H), 7.37−7.31 (m, 3 H), 5.94 (t, $J$ = 7.7 Hz, 1 H), 3.94 (s, 3 H), 3.87 (s, 3 H), 3.76 (br s, 2 H), 2.44 (s, 3 H), 2.07 (quintet, $J$ = 7.6 Hz, 2 H), 1.02 (t, $J$ = 7.5 Hz, 3 H); minor isomer $\delta$ 8.58 (d, $J$ = 2.0 Hz, 1 H), 8.26 (dd, $J$ = 8.4, 2.0 Hz, 1 H), 8.09 (s, 1 H), 7.97 (d, $J$ = 8.4 Hz, 1 H), 7.82 (d, $J$ = 8.3 Hz, 2 H), 7.37−7.31 (m, 2 H), 5.62 (t, $J$ = 7.6 Hz,1 H), 4.32 (br s, 2 H), 3.96 (s, 3 H), 3.88 (s, 3 H), 2.44 (s, 3 H), 1.96 (quintet, $J$ = 7.6 Hz, 2 H), 0.89 (t, $J$ = 7.5 Hz, 3 H); $^{13}C$ NMR (100 MHz, both isomers) $\delta$ 165.6, 165.4, 165.4, 161.8, 161.6, 145.3, 145.0, 144.4, 142.0, 140.3, 139.5, 139.5, 136.5, 134.3, 133.3, 132.6, 132.2, 130.0, 129.9, 129.8, 129.6, 129.5, 129.0, 128.6, 128.2, 128.1, 126.3, 125.8, 55.6, 54.7, 52.7, 52.6, 52.5, 52.5, 21.9, 21.8, 21.6, 21.3, 13.5, 13.2; MS (EI) *m*/*z* 276 (94), 274 (87), 244 (100); HRMS calcd for $C_{16}H_{18}NO_5$ ($M^+$ − Ts) 304.1185, found 304.1178.

Vinyl sulfone: IR (film) 1726, 1704 (sh) $cm^{-1}$; $^1H$ NMR (400 MHz) major isomer $\delta$ 8.56 (s, 1 H), 8.33 (s, 1 H), 8.13 (d, $J$ = 8.2 Hz, 1 H), 7.84 (d, $J$ = 8.0 Hz, 2 H), 7.38 (d, $J$ = 8.0 Hz, 2 H), 6.96 (d, $J$ = 8.2 Hz, 1 H), 6.42 (s, 1 H), 3.96 (s, 3 H), 3.89 (s, 3 H), 2.47 (s, 3 H), 2.14 (t, $J$ = 7.6 Hz, 2 H), 1.56−1.43 (m, 2 H), 0.83 (t, $J$ = 7.3 Hz, 3 H); signals from the minor isomer were observed at $\delta$ 8.69 (s) and 6.45 (s); $^{13}C$ NMR (100 MHz) major isomer $\delta$ 165.5, 165.4, 161.1, 150.9, 145.1, 139.2, 138.3, 133.6, 132.1, 130.2, 129.8, 129.5, 127.9, 127.7, 124.3, 52.6, 52.6, 36.8, 21.6, 20.3, 13.3; MS (EI) *m*/*z* 338 (33), 244 (51), 216 (45), 156 (84), 128 (72), 91 (100); HRMS calcd for $C_{16}H_{18}NO_5$ ($M^+$ − Ts) 304.1185, found 304.1185.

**Adduct 21 (Table 2, Entry 4).** The adduct was obtained as a pale yellow foam. NMR analysis showed the product to be the pure allyl sulfone isomer, obtained as a 2:1 mixture of geometrical isomers: IR (film) 1724, 1688 $cm^{-1}$; $^1H$ NMR (400 MHz) major isomer: 8.55 (d, $J$ = 1.9 Hz, 1 H), 8.43 (s, 1 H), 8.08 (dd, $J$ = 8.2, 1.9 Hz, 1 H), 7.76 (d, $J$ = 8.3 Hz, 2 H), 7.46 (d, $J$ = 8.2 Hz, 1 H), 7.38 (d, $J$ = 8.3 Hz, 2 H), 6.05 (t, $J$ = 7.7 Hz, 1 H), 3.93 (s, 3 H), 3.66 (br s, 2 H), 2.46 (s, 3 H), 1.97 (quintet, $J$ = 7.6 Hz, 2 H), 1.01 (t, $J$ = 7.5 Hz, 3 H); minor isomer: $\delta$ 8.58 (d, $J$ = 1.9 Hz,1 H), 8.19 (s, 1 H), 8.13 (dd, $J$ = 8.3, 1.9 Hz, 1 H), 7.97 (d, $J$ = 8.3 Hz, 1 H), 7.85 (d, $J$ = 8.3 Hz, 2 H), 7.38 (d, $J$ = 8.3 Hz, 2 H), 5.64 (t, $J$ = 7.7 Hz, 1 H), 4.28 (br s, 2 H), 3.95 (s, 3 H), 2.46 (s, 3 H), 1.86 (quintet, $J$ = 7.6 Hz, 2 H), 0.88 (t, $J$ = 7.5 Hz, 3 H); $^{13}C$ NMR (100 MHz, both isomers) $\delta$ 164.8, 164.7, 162.1, 161.8, 146.9, 145.5, 145.0, 142.8, 142.0, 141.4, 140.3, 138.8, 136.3, 136.2, 131.6, 131.6, 131.2, 131.2, 130.7, 130.4, 130.1, 129.9, 128.4, 128.2, 124.8, 124.5, 98.9, 97.3, 54.6, 54.2, 52.6, 52.5, 21.8, 21.6, 21.1, 13.3, 13.2; MS (EI) *m*/*z* 372 (14), 344 (81), 202 (86), 156 (69), 89 (100); HRMS calcd for $C_{14}H_{15}INO_3$ ($M^+$ − Ts) 372.0097, found 372.0109.

**Adduct 22 (Table 2, Entry 5).** Chromatography (hexanes−ethyl acetate, 4:1−2:1) gave 72% of the vinyl sulfone as a pale yellow foam, which NMR analysis showed to be a pure geometrical isomer, along with a further 17% of the vinyl sulfone (total 89%), obtained as a 5:1 mixture of geometrical isomers. The major isomer had: IR (film) 1726, 1699 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 8.60 (s, 1 H), 8.14 (d, $J$ = 8.0 Hz, 1 H), 7.94 (d, $J$ = 8.0 Hz, 1 H), 7.89 (d, $J$ = 8.1 Hz, 2 H), 7.37 (d, $J$ = 8.1 Hz, 2 H), 6.62 (s, 1 H), 4.15 (d, $J$ = 16.4 Hz, 1 H), 3.95 (s, 3 H), 3.60 (d, $J$ = 16.4 Hz, 1 H), 3.23 (s, 3 H), 2.45 (s, 3 H), 2.04 (s, 3 H); $^{13}C$ NMR (100 MHz) $\delta$ 170.5, 164.6, 147.1, 146.2, 144.8, 141.4, 136.8, 131.7, 131.3, 130.1, 129.6, 128.1, 123.3, 101.7, 70.7, 58.6, 52.6, 23.9, 21.6; MS (EI) *m*/*z* 388 (18), 218 (100); HRMS calcd for $C_{14}H_{15}INO_4$ ($M^+$ − Ts) 388.0046, found 388.0045. Anal. Calcd for $C_{21}H_{22}INO_6S$: C, 46.42; H, 4.08; N, 2.58. Found: C, 46.68; H, 3.89; N, 2.55. The X-ray structure of the major isomer and related crystallographic data is provided in the Supporting Information and confirms that it is the vinyl sulfone with the *Z*-configuration. $^1H$ NMR signals from the minor isomer were observed at $\delta$ 8.30 (s) and 6.76 (s).

**Adduct 23 (Table 2, Entry 6).** The adduct was obtained as an orange solid. NMR analysis showed the product to be the vinyl sulfone as a 4.5:1 mixture of geometrical isomers: IR (film) 1727, 1706 $cm^{-1}$; $^1H$ NMR (400 MHz, major isomer) $\delta$ 8.55 (d, $J$ = 2.0 Hz, 1 H), 8.38 (s, 1 H), 8.17 (dd, $J$ = 8.2, 2.0 Hz, 1 H), 7.86 (d, $J$ = 8.2 Hz, 2 H), 7.39 (d, $J$ = 8.2 Hz, 2 H), 7.13 (d, $J$ = 8.2 Hz, 1 H), 6.77 (s, 1 H), 3.98−3.82 (s at $\delta$ 3.95 and 3.87 superimposed on m, total 8 H), 3.23 (s, 3 H), 2.46 (s, 3 H); signals from the minor isomer were observed at $\delta$ 8.68 (s), 8.12 (s), 6.80 (s); $^{13}C$ NMR (100 MHz, major isomer) $\delta$ 165.3, 165.2, 161.2, 146.6, 145.1, 139.1, 138.0, 133.9, 132.0, 130.2, 129.7, 129.5, 128.1, 127.6, 123.3, 70.5, 58.7, 52.6, 52.5, 21.6; MS (EI) *m*/*z* 402 (10), 338 (75), 306 (25), 246 (78), 188 (65), 91 (100); HRMS calcd for $C_{15}H_{16}NO_6$ ($M^+$ − Ts) 306.0978, found 306.0970. Anal. Calcd for $C_{22}H_{23}NO_8S$: C, 57.26; H, 5.02; N, 3.04. Found: C, 56.81; H, 4.86; N, 2.70.

**Adduct 24 (Table 2, Entry 7).** The adduct was obtained as an off-white solid foam. NMR analysis showed the product to be the allyl sulfone isomer as a 2:1 mixture of geometrical isomers. The properties of this product were identical to those of the one obtained via carbonylation of **26** (vide infra).

**Adduct 25 (Table 2, Entry 8).** The adduct was obtained as an off-white solid foam. NMR analysis showed the product to be the allyl sulfone isomer as a 4.5:1 mixture of geometrical isomers: IR (film) 1686, 1629 $cm^{-1}$; $^1H$ NMR (200 MHz, major isomer) $\delta$ 8.36 (s, 1 H), 7.76 (d, $J$ = 8.2 Hz, 2 H), 7.45−7.22 (m, 6 H), 6.74 (d, $J$ = 7.9 Hz, 1 H), 6.68 (d, $J$ = 1.5 Hz, 1 H), 6.62 (dd, $J$ = 7.9, 1.5 Hz, 1 H), 5.93 (s, 2 H), 5.70 (t, $J$ = 7.5 Hz, 1 H), 4.15−2.90 (m, 6 H), 2.54 (t, $J$ = 7.4 Hz, 2 H), 2.43 (s, 3 H), 2.16−1.90 (m, 2 H), 1.68−1.24 (m, 6 H), 1.19 (t, $J$ = 7.2 Hz, 3 H), 1.01 (t, $J$ = 7.1 Hz, 3 H); signals from the minor isomer were observed at $\delta$ 8.30 (s), 7.86 (d, $J$ = 8.2 Hz), 5.82 (t, $J$ = 7.5 Hz); $^{13}C$ NMR (50 MHz, both isomers) $\delta$ 167.8, 162.3, 147.3, 145.3, 144.8, 136.9, 136.6, 136.2, 136.0, 135.0, 132.3, 130.3, 129.7, 129.6, 129.6, 129.4, 128.8, 128.2, 128.0, 127.3, 120.9, 108.6, 107.9, 100.6, 54.8, 42.7, 38.7, 35.4, 31.3, 28.6, 28.1, 21.5, 13.8, 12.7; MS (EI) *m*/*z* 449 (4.5, $M^+$ − Ts), 421 (50), 398 (20), 348 (42), 184 (100); HRMS calcd for $C_{27}H_{33}N_2O_4$ ($M^+$ − Ts) 449.2440, found 449.2432.

**Adduct 26 (Table 2, Entry 9).** The adduct was obtained as a yellow solid foam. NMR analysis showed the product to be the allyl sulfone isomer as a 2:1 mixture of geometrical isomers: IR (film) 1689 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 8.40 (s, major isomer) and 8.18 (s, minor isomer, total 1 H), 7.95−7.75 (m, 3 H), 7.55−7.32 (m, 4 H), 7.17−7.04 (m, 1 H), 6.75−6.55 (m, 3 H), 6.01 (t, $J$ = 7.6 Hz, major isomer) and 5.69 (t, $J$ = 7.5 Hz, minor isomer, total 1 H), 5.93 (s, 2 H), 4.22 (br s, minor isomer) and 3.68 (br s, major isomer, total 2 H), 2.52 (t, $J$ =

7.4 Hz, 2 H), 2.46 (s, 3 H), 1.95−1.15 (m, 8 H); $^{13}$C NMR (50 MHz, both isomers) $\delta$ 162.3, 161.8, 147.4, 145.4, 145.2, 144.8, 142.5, 140.7, 140.1, 138.5, 137.9, 136.9, 136.2, 136.1, 131.4, 131.1, 130.2, 130.1, 130.0, 129.7, 129.3, 128.5, 128.2, 125.3, 124.8, 120.9, 108.7, 108.0, 100.6, 99.7, 97.8, 54.4, 54.1, 35.3, 31.2, 28.7, 28.6, 28.5, 28.0, 27.3, 21.5; MS (EI) *m*/*z* 631 ($M^+$, 0.9), 476 (18), 448 (20), 270 (18), 229 (61), 156 (61), 147 (100); HRMS calcd for $C_{22}H_{23}INO_3$ ($M^+$ − Ts) 476.0723, found 476.0732.

**Conjugate Addition of Aniline 11c to Acetylenic Sulfone 17.** Aniline **11c** (500 mg, 1.22 mmol), $K_2CO_3$ (168 mg, 1.22 mmol), and sulfone **17** (329 mg, 1.83 mmol) were stirred for 6 h in 5 mL of 10:1 DMF−water. The mixture was diluted with dichloromethane, filtered, and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 3:1−2:1) gave 646 mg (90%) of **27** as a bright yellow foam. NMR analysis showed the product to be a 5:1 mixture of *Z* and *E* geometrical isomers: IR (film) 1725 cm$^{-1}$; $^1$H NMR (400 MHz, major isomer) $\delta$ 8.29 (d, $J$ = 1.8 Hz, 1 H), 7.98 (dd, $J$ = 8.2, 1.8 Hz, 1 H), 7.46 (d, $J$ = 8.5 Hz, 1 H), 7.33 (d, $J$ = 10.6 Hz, 1 H), 7.32−7.13 (m, 9 H), 5.73 (d, $J$ = 10.6 Hz, 1 H), 5.26−5.12 (m, 2 H), 3.92 (s, 3 H), 2.38 (s, 3 H); signals from the minor isomer were observed at $\delta$ 8.52 (d, $J$ = 1.8 Hz), 8.39 (d, $J$ = 13.6 Hz), 8.05 (dd, $J$ = 8.2, 1.8 Hz), 7.70 (d, $J$ = 8.3 Hz), 5.06 (d, $J$ = 13.6 Hz); $^{13}$C NMR (100 MHz, major isomer) $\delta$ 164.7, 152.8, 144.6, 143.8, 140.2, 138.6, 134.5, 134.2, 131.4, 131.2, 129.6, 129.3, 128.4, 127.9, 126.3, 111.9, 99.2, 69.5, 52.4, 21.4; MS (EI) *m*/*z* 591 (0.6), 560 (1), 436 (14), 390 (37), 264 (46), 204 (63), 114 (77), 91 (100); HRMS calcd for $C_{18}H_{15}INO_4$ ($M^+$ − Ts) 436.0046, found 436.0069.

**Conjugate Addition of Aniline 11a to Dienyl Sulfone 18.** A mixture of aniline **11a** (128 mg, 0.421 mmol), $K_2CO_3$ (58 mg, 0.42 mmol), and sulfone **18** (105 mg, 0.504 mmol) was stirred for 4 d at room temperature in 0.5 mL of 10:1 DMF−water. The mixture was then partitioned between ether and water, the aqueous layer was washed with ether, and the combined organic fractions were dried and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 4:1−1:1) gave 19.4 mg of recovered **11a**, 12.8 mg of recovered **18**, and 145 mg (67%; 79% based on recovered **11a**) of **28** as a bright yellow foam. NMR analysis showed the product to be an 8:1 mixture of *E* and *Z* geometrical isomers: IR (film) 1724, 1681 cm$^{-1}$; $^1$H NMR (400 MHz, major isomer) $\delta$ 8.60 (d, $J$ = 1.9 Hz, 1 H), 8.12 (s, 1 H), 8.07 (dd, $J$ = 8.1, 1.9 Hz, 1 H), 7.66 (d, $J$ = 8.3 Hz, 2 H), 7.32 (d, $J$ = 8.3 Hz, 2 H), 7.22 (d, $J$ = 8.1 Hz, 1 H), 5.69 (dt, $J$ = 15.4, 6.5 Hz, 1 H), 5.55 (dt, $J$ = 15.4, 7.3 Hz, 1 H), 4.32−4.25 (br m, 2 H), 3.96 (s, 3 H), 3.73 (d, $J$ = 7.3 Hz, 2 H), 2.46 (s, 3 H); signals from the minor isomer were observed at $\delta$ 8.29 (s), 5.78 (m); $^{13}$C NMR (100 MHz, major isomer) $\delta$ 164.5, 161.9, 145.8, 144.8, 141.3, 135.4, 133.4, 131.7, 130.6, 129.7, 129.7, 128.2, 121.2, 99.0, 59.3, 52.6, 47.2, 21.5; MS (EI) *m*/*z* 358 (9), 330 (77), 288 (31), 202 (100); HRMS calcd for $C_{13}H_{13}INO_3$ ($M^+$ − Ts) 357.9940, found 357.9909.

**Conjugate Addition of Aniline 11c to Dienyl Sulfone 18.** A mixture of aniline **11c** (173 mg, 0.421 mmol), $K_2CO_3$ (58 mg, 0.42 mmol), and sulfone **18** (105 mg, 0.503 mmol) was stirred for 4 d at room temperature in 0.5 mL of 10:1 DMF−water. The mixture was then partitioned between ether and water. The aqueous layer was washed with ether, and the combined organic fractions were dried and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 4:1−1:1) gave 37.1 mg of recovered **11c**, 15.9 mg of recovered **18**, and 163 mg (63%; 80% based on recovered **11c**) of **29** as a bright yellow foam, obtained as the pure *E*-isomer: IR (film) 1712 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 8.53 (d, $J$ = 1.9 Hz, 1 H), 7.99 (dd, $J$ = 8.2, 1.9 Hz, 1 H), 7.65 (*d*, $J$ = 8.2 Hz, 2 H), 7.46−7.15 (m, 7 H), 7.14 (d, $J$ = 8.2 Hz, 1 H), 5.81−5.70 (m, 1 H), 5.50 (dt, $J$ = 15.4, 7.4 Hz, 1 H), 5.10 (br s, 2 H), 4.51 (dd, $J$ = 15.4, 5.6 Hz, 1 H), 3.93 (s, 3 H), 3.78 (dd, $J$ = 15.4, 7.1 Hz, 1 H), 3.74 (d, $J$ = 7.4 Hz, 2 H), 2.43 (s, 3 H); $^{13}$C NMR (50 MHz) $\delta$ 164.8, 154.1, 147.2, 144.8, 140.8, 135.9, 135.5, 134.6, 130.8, 130.4, 129.7, 128.3, 127.9, 127.7, 120.6, 118.6, 99.9, 67.8, 59.5, 52.5, 51.3, 21.6; MS (FAB) *m*/*z* 620 (7, $M^+$ + 1), 307 (22), 154 (100); HRMS calcd for $C_{20}H_{19}INO_4$ ($M^+$ − Ts) 464.0359, found 464.0350.

**Preparation of 6 by Carbonylation of 19.** Adduct **19** (140 mg, 0.281 mmol), triethylamine (39 $\mu$L, 0.28 mmol), and $Pd(OAc)_2$ (6.3 mg, 0.028 mmol) were stirred in 30 mL of methanol at 70 °C for 2 d in a Parr high-pressure reaction vessel under carbon monoxide at a pressure of 27 atm (400 psi). The apparatus was cooled to room temperature and vented, and the mixture was filtered and then concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 4:1−1:1) gave 31.0 mg (22%) of recovered **19** and 88.1 mg (73%; 94% based on recovered starting material) of **6** as a pale yellow solid foam. NMR analysis showed the product to be a 2:1 mixture of geometrical isomers. The product was identical to that obtained by direct addition of **4b** to **5** (vide supra).

**Preparation of 20 by Carbonylation of 21.** Adduct **21** was converted into **20** in 94% yield as in the preceding procedure: pale yellow solid foam. NMR analysis showed the product to be a 2:1 mixture of geometrical isomers. The product was identical to that obtained by direct addition of **12** to **14** (vide supra).

**Preparation of 24 by Carbonylation of 26.** Adduct **26** was treated as in the preparation of **6** to afford 14% of recovered **26** and 82% (95% based on recovered starting material) of **24** as an off-white solid foam. NMR analysis showed the product to be a 2:1 mixture of geometrical isomers: IR (film) 1727, 1687 cm$^{-1}$; $^1$H NMR (200 MHz) $\delta$ 8.36 (s, major isomer) and 8.12 (s, minor isomer, total 1 H), 7.94−7.24 (m, 8 H), 6.75−6.56 (m, 3 H), 5.92 (s, major isomer) and 5.91 (s, minor isomer, total 2 H), 5.86 (t, $J$ = 7.5 Hz, major isomer) and 5.61 (t, $J$ = 7.5 Hz, minor isomer, total 1 H), 4.27 (s, minor isomer) and 3.72 (s, major isomer, total 2 H), 3.82 (s, both isomers, 3 H), 2.56−2.43 (s at $\delta$ 2.44 superimposed on m, total 5 H), 2.01−1.77 (m, 2 H), 1.70−1.13 (m, 6 H); $^{13}$C NMR (50 MHz, both isomers) $\delta$ 166.1, 166.0, 161.8, 161.7, 147.4, 147.3, 145.4, 145.3, 145.1, 144.7, 140.1, 137.1, 136.8, 136.4, 136.2, 136.0, 135.6, 133.5, 132.6, 131.1, 131.0, 130.2, 129.9, 129.7, 129.5, 129.5, 129.1, 128.3, 128.1, 126.5, 126.4, 120.8, 108.6, 107.9, 100.6, 55.1, 54.5, 52.4, 52.2, 35.4, 31.2, 28.7, 28.5, 28.1, 27.5, 21.5; MS (EI) *m*/*z* 504 (1.5), 408 (21), 380 (94), 357 (29), 348 (36), 184 (72), 147 (100); HRMS calcd for $C_{24}H_{26}NO_5$ ($M^+$ − Ts) 408.1811, found 408.1792.

**Preparation of 33 by Carbonylation of 27.** Adduct **27** was converted into **33** as in the case of **6** to afford 73% of **33** as a yellow solid foam, obtained exclusively as the *E* isomer: IR (film) 1727, 1623 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 8.70 (d, $J$ = 2.0 Hz, 1 H), 8.43 (d, $J$ = 13.7 Hz, 1 H), 8.25 (dd, $J$ = 8.2, 2.0 Hz, 1 H), 7.66 (d, $J$ = 8.3 Hz, 2 H), 7.38−7.07 (m, 8 H), 5.36−4.99 (br m, 2 H), 5.05 (d, $J$ = 13.7 Hz, 1 H), 3.96 (s, 3 H), 3.58 (br s, 3 H), 2.40 (s, 3 H); $^{13}$C NMR (50 MHz) $\delta$ 165.0, 163.6, 152.2, 143.6, 141.9, 140.2, 139.0, 134.8, 134.7, 133.6, 131.4, 130.2, 129.6, 128.6, 128.5, 128.3, 128.1, 127.0, 110.3, 69.3, 52.7, 52.5, 21.5; MS (EI) *m*/*z* 523 ($M^+$, 0.3), 389 (7), 324 (10), 91 (100); HRMS calcd for $C_{20}H_{18}NO_6$ ($M^+$ − Ts) 368.1134, found 368.1110.

**4-Quinolone 30.** Ester **6** (662 mg, 1.54 mmol) was dissolved in 15 mL of THF. The solution was cooled to −78 °C, and LiHMDS (11.5 mL, 0.267 M, 3.07 mmol) was added. The resulting red solution was stirred for 70 min at −78 °C, and the reaction was quenched with saturated $(NH_4)_2SO_4$ solution. The mixture was partitioned between ether and dilute $(NH_4)_2SO_4$ solution. The aqueous layer was washed with ether, and the combined organic fractions were dried and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 2:1) gave 473 mg (77%) of a single geometrical isomer of **30** as a white solid: mp 149−152 °C; IR (film) 1682 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 8.67 (br s, 1 H), 8.49−8.08 (br s, 1 H), 8.00 (d, $J$ = 7.5 Hz, 1 H), 7.71 (d, $J$ = 8.1 Hz, 2 H), 7.64 (t, $J$ = 7.5 Hz, 1 H), 7.34 (d, $J$ = 8.1 Hz, 2 H), 7.25 (t, $J$ = 7.5 Hz, 1 H), 5.97 (t, $J$ = 7.6 Hz, 1 H), 4.97 (s, 1 H), 2.44 (s, 3 H), 2.22−1.85 (m, 2 H), 1.42−1.21 (m, 4 H), 0.89 (t, $J$ = 6.7 Hz, 3 H); $^{13}$C NMR (100 MHz) $\delta$ 182.8, 161.3, 145.9, 136.3, 134.6, 129.8, 129.2, 128.0, 125.0, 122.1, 71.6, 30.8, 26.4, 22.2, 21.6, 13.7; MS (EI) *m*/*z* 276

(42), 248 (100); MS (ESI) *m*/*z* 420 ($M^+ + Na$); HRMS calcd for $C_{21}H_{23}NO_3S$ ($M^+ - CO$) 369.1399, found 369.1373. Anal. Calcd for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.52. Found: C, 66.37; H, 5.62; N, 3.52.

**4-Quinolone 31.** Ester **20** (68.3 mg, 0.149 mmol) was dissolved in 2 mL of THF. The solution was cooled to −78 °C, and LiHMDS (2.00 mL, 0.148 M, 0.296 mmol) was added. The resulting red solution was stirred for 60 min at −78 °C, and the reaction was quenched with saturated $(NH_4)_2SO_4$ solution. The mixture was partitioned between ether and water. The aqueous layer was washed with ether, and the combined organic fractions were dried and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 2:1) gave 49.8 mg (78%) of a single geometrical isomer of **31** as an off-white solid: mp 167−170 °C dec; IR (film) 1722, 1690 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 8.70 (br s, 1 H), 8.63 (t, $J$ = 1.2 Hz, 1 H), 8.36−8.22 (m, 2 H), 7.68 (d, $J$ = 8.2 Hz, 2 H), 7.34 (d, $J$ = 8.2 Hz, 2 H), 6.00 (t, $J$ = 7.7 Hz, 1 H), 5.01 (s, 1 H), 3.93 (s, 3 H), 2.43 (s, 3 H), 2.20−1.99 (m, 2 H), 1.02 (t, $J$ = 7.5 Hz, 3 H); $^{13}C$ NMR (50 MHz) $\delta$ 182.2, 165.2, 161.3, 146.1, 143.9, 136.8, 136.3, 134.4, 129.9, 129.8, 129.1, 126.8, 121.8, 120.6, 71.4, 52.3, 21.7, 20.4, 13.3; MS (EI) *m*/*z* 334 (47), 306 (100); HRMS calcd for $C_{21}H_{21}NO_5S$ ($M^+ - CO$) 399.1140, found 399.1151. Anal. Calcd for $C_{22}H_{21}NO_6S$: C, 61.81; H, 4.95; N, 3.28. Found: C, 61.80; H, 4.88; N, 3.29. See the Supporting Information for the X-ray structure of **31**.

**4-Quinolone 32.** Ester **24** (1.043 g, 1.850 mmol) was dissolved in 15 mL of THF. The solution was cooled to −78 °C, and LiHMDS (13.9 mL, 0.267 M, 3.71 mmol) was added. The resulting red solution was stirred for 70 min at −78 °C, and the reaction was quenched with saturated $(NH_4)_2SO_4$ solution. The mixture was partitioned between ether and dilute $(NH_4)_2SO_4$ solution. The aqueous layer was washed with ether, and the combined organic fractions were dried and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 2:1) gave 928 mg (94%) of a single geometrical isomer of **32** as a white solid foam: IR (film) 1684 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 8.66 (br s, 1 H), 8.21 (br s, 1 H), 8.00 (d, $J$ = 7.7 Hz, 1 H), 7.78−7.58 (m, 3 H), 7.40−7.20 (m, 3 H), 6.72 (d, $J$ = 7.7 Hz, 1 H), 6.65 (s, 1 H), 6.60 (d, $J$ = 7.7 Hz, 1 H), 5.96 (t, $J$ = 7.7 Hz, 1 H), 5.93 (s, 2 H), 4.95 (s, 1 H), 2.51 (t, $J$ = 7.5 Hz, 2 H), 2.43 (s, 3 H), 2.22−1.91 (m, 2 H), 1.69−1.20 (m, 6 H); a 10% nOe was observed between the proton at C-3 ($\delta$ 4.95 ppm) and the allylic side chain protons ($\delta$ 2.2 ppm), indicating the *E* geometry; $^{13}C$ NMR (50 MHz) $\delta$ 182.8, 161.2, 147.4, 145.8, 145.4, 136.3, 136.1, 134.6, 129.8, 129.2, 128.0, 125.0, 122.0, 120.9, 108.7, 108.0, 100.7, 71.7, 35.4, 31.3, 28.6, 28.5, 26.7, 21.6; MS (EI) *m*/*z* 348 (7), 276 (38), 248 (100); HRMS calcd for $C_{29}H_{29}NO_5S$ ($M^+ - CO$) 503.1767, found 503.1756. Anal. Calcd for $C_{30}H_{29}NO_6S$: C, 67.78; H, 5.50; N, 2.63. Found: C, 68.34; H, 5.66; N, 2.73.

**4-Quinolone 34.** 2,2,6,6-Tetramethylpiperidine (364 $\mu$L, 2.16 mmol) was dissolved in 5 mL of THF. The solution was cooled to −78 °C, and *tert*-butyllithium (1.06 mL, 1.7 M, 1.8 mmol) was added dropwise. The solution was removed from the cooling bath, stirred at room temperature for 30 min, and then cooled back to −78 °C. A solution of diester **23** (332 mg, 0.719 mmol) in 3 mL of THF was added via cannula. The deep red solution was slowly warmed to room temperature and stirred for 3 days. The mixture was diluted with dichloromethane, quenched with water, and washed with 10% HCl solution. The aqueous layer was washed with dichloromethane, and the combined organic layers were dried and concentrated in vacuo to afford 289 mg (100%) of **34** as a homogeneous oil (NMR, TLC) that crystallized from dichloromethane and ether to provide **34** as an off-white solid: mp 246−247 °C; IR (film) 1722, $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 9.91 (br s, 1 H, exchanged $D_2O$), 8.86 (d, $J$ = 1.8 Hz, 1 H), 8.22 (dd, $J$ = 8.6, 1.8 Hz, 1 H), 7.99 (d, $J$ = 8.2 Hz, 2 H), 7.46 (d, $J$ = 8.6 Hz, 1 H), 7.27 (d, $J$ = 8.2 Hz, 2 H), 5.26 (s, 2 H), 3.88 (s, 3 H), 3.66 (s, 3 H), 2.38 (s, 3 H); $^{13}C$ NMR (100 MHz) $\delta$ 173.0, 165.7, 152.9, 144.1, 140.1, 139.0, 133.5, 129.1, 128.9, 128.3, 127.3, 125.6, 118.3, 118.2, 68.4, 59.5, 52.3, 21.6; MS (EI) *m*/*z* 337 (30), 336 (85), 306 (100); HRMS calcd for $C_{20}H_{18}NO_4$ ($M^+ - SO_2H$) 336.1236, found 336.1250. Anal. Calcd for $C_{20}H_{19}NO_6S$: C, 59.84; H, 4.77; N, 3.49. Found: C, 59.69; H, 4.82; N, 3.37.

**Alkaloid 1.** Mercuric chloride (120 mg, 0.44 mmol) was dissolved in 6 mL of 2:1 methanol−THF. Thin strips of aluminum metal (50 mg, 1.9 mg atom) were added, and the mixture was stirred for 5 min, whereupon keto sulfone **30** (99.9 mg, 0.251 mmol) was added in one portion. The mixture was stirred for 90 min at room temperature and allowed to settle, and the supernatant liquid was decanted and diluted with dichloromethane. It was washed with 10% HCl solution, and the aqueous layer was neutralized with saturated $NaHCO_3$ solution, and extracted three times with dichloromethane. The combined organic layers were dried and evaporated. Chromatography (chloroform−methanol, 40:1−10:1) gave 36.5 mg (68%) of **1** as a white solid: mp 141−142 °C (from 1:1 benzene/hexanes) (lit.[12a] mp 141−142 °C); IR (film) 1638, 1594, 1550, 1503 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 8.37 (dd, $J$ = 8.1, 1.2 Hz, 1 H), 7.81 (d, $J$ = 8.1 Hz, 1 H), 7.58 (td, $J$ = 7.6, 1.2 Hz, 1 H), 7.33 (t, $J$ = 7.6 Hz, 1 H), 6.25 (s, 1 H), 2.70 (t, $J$ = 7.8 Hz, 2 H), 1.79−1.63 (m, 2 H), 1.32−1.16 (m, 4 H), 0.79 (t, $J$ = 7.0 Hz, 3 H); $^{13}C$ NMR (100 MHz) $\delta$ 178.8, 155.4, 140.7, 131.7, 125.2, 124.9, 123.6, 118.6, 108.1, 34.3, 31.3, 28.7, 22.3, 13.8; MS (EI) *m*/*z* (%) 215 (2, $M^+$), 184 (29), 172 (79), 158 (99), 130 (100); HRMS calcd for $C_{14}H_{17}NO$ 215.1310, found 215.1321. The spectra were in agreement with the literature.[12a] The X-ray structure of **1** iand related data are provided in the Supporting Information.

***Ruta chalepensis* Alkaloid 2.** Keto sulfone **32** (57.5 mg, 0.108 mmol) was subjected to the preceding procedure to afford 25.6 mg (68%) of **2** as a white solid: mp 156−157 °C (from dichloromethane) (lit.[15] mp 163 °C); IR (film) 1635, 1594, 1548, 1501 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 12.35 (br s, 1 H), 8.36 (dd, $J$ = 8.1, 1.3 Hz, 1 H), 7.73 (d, $J$ = 8.0 Hz, 1 H), 7.58 (ddd, $J$ = 8.0, 7.0, 1.3 Hz, 1 H), 7.31 (ddd, $J$ = 8.1, 7.0, 1.0 Hz, 1 H); 6.67 (d, $J$ = 7.9 Hz, 1 H), 6.59 (d, $J$ = 1.5 Hz, 1 H), 6.52 (dd, $J$ = 7.9, 1.5 Hz, 1 H), 6.27 (s, 1 H), 5.87 (s, 2 H), 2.71 (t, $J$ = 7.7 Hz, 2 H), 2.41 (t, $J$ = 7.5 Hz, 2 H), 1.80−1.63 (m, 2 H), 1.54−1.38 (m, 2 H), 1.38−1.15 (m, 4 H); $^{13}C$ NMR (100 MHz) $\delta$ 178.8, 155.5, 147.4, 145.4, 140.7, 136.3, 131.7, 125.1, 124.9, 123.5, 120.9, 118.7, 108.7, 108.0, 108.0, 100.6, 35.5, 34.3, 31.4, 29.1, 29.0, 28.8; MS (EI) *m*/*z* 349 (0.8, $M^+$), 184 (19), 172 (100); HRMS calcd for $C_{22}H_{23}NO_3$ 349.1678, found 349.1699. Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.46; H, 6.13; N, 3.98. The spectra were in agreement with those reported[15] for the natural product.

***Ruta chalepensis* Alkaloid 3.** Sodium bicarbonate (15.5 mg, 0.185 mmol) and dimethyl sulfate (17.4 $\mu$L, 0.184 mmol) were added to a solution of **2** (32.2 mg, 0.0922 mmol) in 5 mL of THF. The mixture was stirred at room temperature for 1 h and then refluxed for 17 h. The mixture was then partitioned between brine and ether. The aqueous layer was washed with ether, and the combined organic fractions were dried and concentrated in vacuo. Chromatography (hexanes−ethyl acetate, 4:1−2:1) gave 13.9 mg of **2** as a yellow oil. Elution of the column with dichloromethane−methanol, 10:1, followed by rechromatography of the product with chloroform−methanol, 40:1, gave another 11.2 mg of **2** (total yield, 75%) as a yellow oil: IR 1595, 1503, 1485, 1246 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 8.14 (dd, $J$ = 8.2, 1.5 Hz, 1 H), 7.98 (d, $J$ = 8.4 Hz, 1 H), 7.66 (ddd, $J$ = 8.4, 6.9, 1.5 Hz, 1 H), 7.44 (ddd, $J$ = 8.2, 6.9, 1.2 Hz, 1 H), 6.72 (d, $J$ = 7.7 Hz, 1 H), 6.67 (d, $J$ = 1.5 Hz, 1 H), 6.63 (s, 1 H), 6.61 (dd, $J$ = 7.7, 1.5 Hz, 1 H), 5.92 (s, 2 H), 4.04 (s, 3 H), 2.92 (t, $J$ = 7.9 Hz, 2 H), 2.53 (t, $J$ = 7.4 Hz, 2 H), 1.90−1.25 (m, 8 H);$^{13}C$ NMR (50 MHz) $\delta$ 164.1, 162.3, 148.7, 147.4, 145.3, 136.6, 129.6, 128.2, 124.7, 121.5, 121.0, 120.0, 108.8, 108.0, 100.6, 99.7, 55.5, 39.9, 35.6, 31.6, 30.0, 29.4, 29.0; MS (EI) *m*/*z* 363 (2, $M^+$), 306 (2), 228 (6), 186 (100); HRMS calcd for $C_{23}H_{25}NO_3$ 363.1834, found 363.1861. The spectra were in agreement with those reported[15] for the natural product.

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**Supporting Information Available:** Procedures for the preparation of compounds **11a**,**b**, **12**, and **16**, X-ray data for compounds **1**, **22**, and **31**, and copies of $^{1}H$ and $^{13}C$ NMR spectra of new compounds and of alkaloids **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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