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Enantioselective Formal [3+3] Annulation for the Direct Construction of Bicyclic Skeletons with Four Stereogenic Centers

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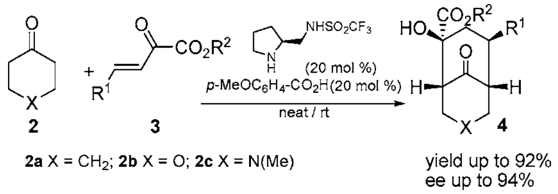
ABSTRACT



An enantioselective formal [3+3] annulation reaction of cyclic ketones with enones has been developed. In the presence of 20 mol % of pyrrolidine-thiourea 1a or *N*-(pyrrolidin-2-ylmethyl)trifluoromethanesulfonamide 1i, the reactions afford bicyclo [3.3.1] adducts in moderate to good yields with good to high enantioselectivities under mild conditions.

Tandem reactions are powerful synthetic tools for rapid creation of complex molecules with multiple stereogenic centers.[1] Of the developed strategies for asymmetric tandem reactions, organocatalysis[2] provides an efficient protocol with environmental friendliness, operational simplicity, and atom economy. Although several elegant organocatalytic tandem reactions have been reported recently,[3,4] the construction of cyclic molecules with four or more stereogenic centers[4] in a cascade manner remains a challenge. In this Letter, we disclose the first example of an asymmetric formal [3+3] annulation reaction of cyclic ketones with enones, resulting in the formation of two new C−C bonds and four stereogenic centers with high enantioselectivity under mild conditions.

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(1) For recent reviews on tandem reactions, see: (a) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Guo, H.; Ma, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (d) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619. (e) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143. (f) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (g) Tejedor, D.; Gonzalez-Cruz, D.; Santos-Exposito, A.; Marrero-Tellado, J. J.; de Armas, P.; Garcia-Tellado, F. *Chem. Eur. J.* **2005**, *11*, 3502.

(2) For books and selected recent reviews on organocatalysis, see: (a) Lelais, D. W.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79. (b) Ballini, R.; Bosica, G.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (d) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2005. (e) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (f) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (g) Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526. (h) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (i) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542. (j) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580. (k) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611. (l) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621.

(3) For a review, see: Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. For selected recent examples on organocatalytic tandem reactions, see: (a) Zu, L.-S.; Wang, J.; Li, H.; Xie, H.-X.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036. (b) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.-S.; Jiang, W.; Wei, S.-H.; Wang, W. *Chem. Commun.* **2007**, 878. (c) Wang, W.; Li, H.; Wang, J.; Zu, L.-S. *J. Am. Chem. Soc.* **2006**, *128*, 10354. (d) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986. (e) Wang, Y.; Liu, X.-F.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (f) Huang, Y.; Walji, A. M.; Larsen, C. H.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (g) Yang, W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (h) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343. (i) Marigo, M.; Schulte, T.; Franzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710.

(4) (a) Enders, D.; Hüttl, M. R. M.; Runsink, J.; Raabe, G.; Wendt, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 467. (b) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (c) Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475. (d) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272.

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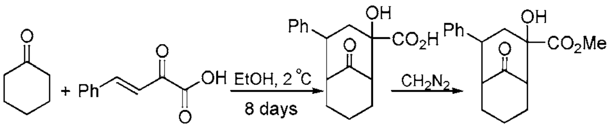
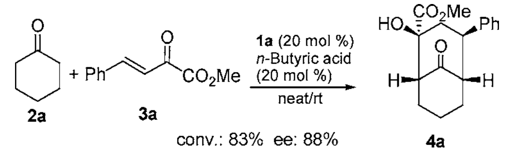
In 1959, Jung reported a reaction of cyclohexanone with enone acids in the presence of KOH, leading to a racemic bicyclic [3.3.1] compound after 8 days.[5] Since this pioneering work, there have been several other studies on this reaction and its chemical transformation (eq 1).[6] To the best of our knowledge, however, none of these investigations has explored the possibility of the asymmetric reactions. We have previously developed a pyrrolidine-thiourea **1a**[7a,c] as an organocatalyst for asymmetric Michael addition. We envisioned that this chiral thiourea[7] is a potential catalyst for the aforementioned reaction. After many attempts, we were pleased to find that the reaction of cyclohexanone with enone **3a** proceeded well to give 2-hydroxy-9-oxo-bicyclo[3.3.1]-nonane **4a** in good conversion with 88% enantiomeric excess as shown in Scheme 1. The relative configurations have been determined by X-ray diffration analysis on compound **4a** (see the Supporting Information). To further improve the conversion and enantioselectivity, several L-proline derivatives **1a**–**i** (Figure 1) have been screened and the results were summarized in Table 1. It was found that both pyrrolidine-thiourea **1a** and pyrrolidine-urea **1b** could promote this reaction in good conversion with high ee values (entries 1 and 2, Table 1). The reaction was very sluggish when proline derivatives **1c**–**e**[8,9] were used (entries 3–5, Table 1). L-Proline **1f**[10] worked well but with only 23% ee (entry 7, Table 1). When **1g**[11] and **1h**[12] were employed as the catalysts (entries 8 and 9, Table 1), moderate conversion and enantioselectivity were observed. To our delight, the product was obtained in 99% conversion with 90% ee when *N*-(pyrrolidin-2-ylmethyl)trifluoromethanesulfonamide **1i**[12] was used in the presence of 20 mol % of *n*-butyric acid (entry 10, Table 1).



(1)

Scheme 1. Pyrrolidine-thiourea **1a** Catalyzed Formal [3+3] Annulation Reaction



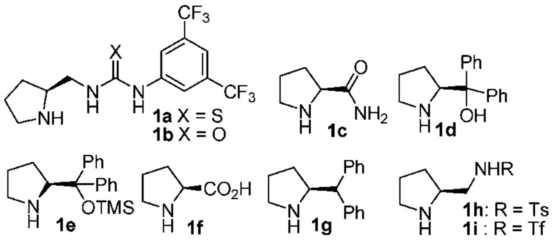
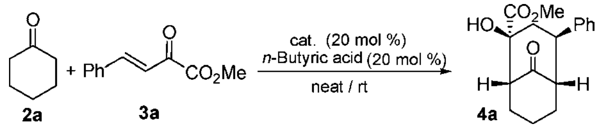


Figure 1. Organocatalysts screened.

Table 1. Effects of Catalysts on the Reaction of Cyclohexanone **2a** and Enone **3a**[a]



entry	catalyst	time (day)	conv[b] (%)[13]	ee[c] (%)
1	**1a**[d]	2	80	88
2	**1b**[d]	2	99	85
3	**1c**	3.5	<5	
4	**1d**	3.5	<5	
5	**1e**	3.5	<5	
6	**1f**	3.5	20	
7[e]	**1f**	3	61[f]	23
8	**1g**	2	53	66
9	**1h**	2	50	85
10	**1i**	2	99	90
11[g]	**1i**	2	89	90
12[h]	**1i**	2	45	90
13[d]	**1i**	2	99 (80[f])	90

[a] Unless otherwise noted, all reactions were carried out at room temperature, cat. **1** (20 mol %), *n*-butyric acid (20 mol %), **2a** (980 mg, 10 mmol), **3a** (0.20 mmol). [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC analysis. [d] In the presence of 4-methoxybenzonic acid (20 mol %). [e] DMSO as a solvent. [f] Isolated yield. [g] Without *n*-butyric acid. [h] 0 °C.

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[5] Jung, L. *Hebd Seances Acad. Sci.* **1959**, *249*, 711.

[6] (a) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Liao, J.-H. *Org. Lett.* **2006**, *8*, 2217. (b) Peters, J. A. *Synthesis* **1979**, 321. (c) Nenajdenko, V. G.; Druzhinin, S. V.; Balenkova, E. S. *Russ. Chem. Bull.* **2004**, *53*, 435. (d) Jung, L. *Bull. Soc. Chim.* **1967**, 4696. (e) Jung, L. *Hebd Seances Acad. Sci. Ser C* **1967**, *265*, 34.

[7] (a) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065. (b) Cao, C.-L.; Sun, X.-L.; Zhou, J.-L.; Tang, Y. *J. Org. Chem.* **2007**, *72*, 4073. (c) Cao, Y.-J.; Lai, Y.-Y.; Wang, X.; Li, Y.-J.; Xiao, W.-J. *Tetrahedron Lett.* **2007**, *48*, 21. (d) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901. (e) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451.

[8] (a) Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc.* **2006**, *128*, 7442. (b) Samanta, S.; Zhao, C.-G. *Tetrahedron Lett.* **2006**, *45*, 3383.

[9] (a) Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1983. (b) Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778. (c) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804. (d) Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 1760. (e) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (f) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (g) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703.

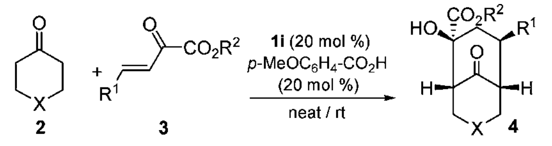
[10] (a) Utsumi, N.; Zhang, H.-L.; Tanaka, F.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2007**, *46*, 1878. (b) Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc.* **2006**, *128*, 7442. (c) Mauksch, M.; Tsogoeva, S. B.; Martynova, I. M.; Wei, S.-W. *Angew. Chem., Int. Ed.* **2007**, *46*, 393. (d) Ward, D. E.; Jheengut, V.; Akinnusi, O. L. *Org. Lett.* **2005**, *7*, 1181. (e) Ward, D. E.; Jheengut, V. *Tetrahedron Lett.* **2004**, *45*, 8347. (f) Enders, D.; Seki, A. *Synlett* **2002**, *1*, 26. (g) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. (h) list, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (i) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

[11] (a) Reyes, E.; Vicario, J. L.; Badia, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135. (b) Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596. (c) Bailey, D. J.; O'Hagan, D.; Tavasli, M. *Tetrahedron: Asymmetry* **1997**, *8*, 149.

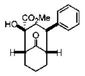
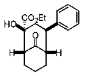
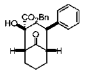
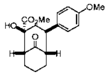
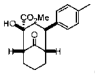
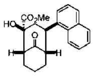
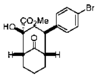
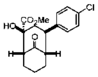
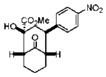
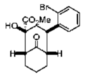
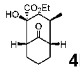
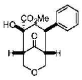
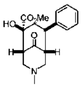
In the absence of acid, **1i** also gave the same enantioselectivity but with a slight reduction of the reaction rate (entry 11, Table 1). Lowering the reaction temperature to 0 °C decreased the conversion significantly (entry 12). By using 4-methoxybenzoic acid instead of *n*-butyric acid, the same ee was achieved (entry 13, Table 1).

Under the optimal conditions, various ketones **2** and enones **3** were examined to investigate the reaction scope. As shown in Table 2, the ester groups in **3** have less effect on the yields and enantioselectivities (entries 1−3, Table 2).

Table 2. Formal [3+3] Asymmetric Reaction of Ketones **2** and Enones **3**^{a}



2a X = CH_2; **2b** X = O; **2c** X = N(Me)

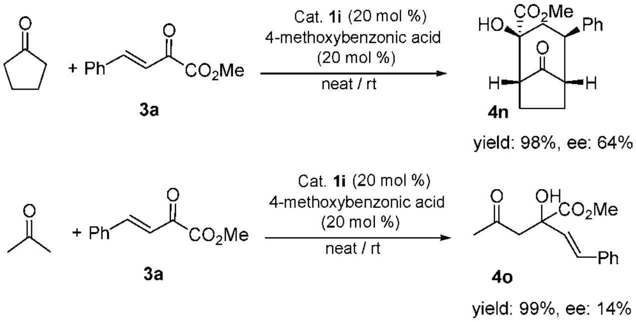
entry	product **4**	time (h)	yield ^{b} (%)	ee ^{c} (%)
1	 **4a**	48	80	90
2	 **4b**	40	74	91
3	 **4c**	24	76	91
4	 **4d**	64	77	87
5	 **4e**	40	80	90
6	 **4f**	50	73	91
7	 **4g**	24	77	90(>99)
8	 **4h**	40	85	93
9	 **4i**	120	90	92
10^d	 **4j**	48	74	93
11	 **4k**	60	56	94
12	 **4l**	7 days	66	90
13^d	 **4m**	72	92	80

^{a} Unless otherwise noted, all reactions were carried out in neat with **2** (980 mg, 10 mmol) and **3** (0.20 mmol) in the presence of **1i** (9.3 mg, 0.04 mmol) and 20 mol % of 4-methoxybenzoic acid. ^{b} Isolated yield. ^{c} Determined by chiral HPLC analysis. ^{d} At 0 °C.

β-Aryl-substituted enones **3** were good substrates to afford the desired products in good yields with high enantioselectivities (entries 4−10, Table 2). While (*E*)-ethyl 4-phenyl-2-oxopent-3-enoate gave the corresponding product **4b** in 74% yield with 91% ee, (*E*)-ethyl 2-oxopent-3-enoate also gave the adduct **4k** in good yield with 94% ee (entry 11, Table 2). Substituents on the benzene ring of *β*-aryl enones **3** influenced slightly the enantioselectivities (86−93% ee). Besides cyclohexanone, its derivatives **2b**−**c** could also give the corresponding products in good yields with high enantioselectivities (entries 12 and 13, Table 2), providing an easy access to optically active heterocyclic compounds with four stereocenters. Noticeably, the optically pure product **4g** (>99% ee) could be obtained through a recrystallization in ether. The relative and absolute configurations have been determined by X-ray diffraction analysis on compounds **4a** and **4g** (see the Supporting Information).[14] The hydroxyl group and the aryl group are located in the *cis*-position. The absolute configuration of **4g** is assigned as 1R, 2S, 4R, 5S by X-ray analysis (see the Supporting Information).

The asymmetric reaction of cyclopentanone and acetone with **3a** using **1i** as catalyst was also investigated. As shown in Scheme 2, cyclopentanone gave the desired bicycle compound in high yield with 64% ee. In the case of acetone, only the aldol product **4o** was obtained in high yield with only 14% ee.

Scheme 2. Reaction of Cyclopentanone and Acetone with **3a**



yield: 98%, ee: 64%

yield: 99%, ee: 14%

The present reaction provides an easy access to compounds with bicyclic [3.3.1] skeleton, many of which are associated with natural products.[15] In addition, compound **4a** could be easily converted to bicyclic [3.3.2] compound **6** in 83% yield with high diastereoselectivity by Baeyer−Village oxidation

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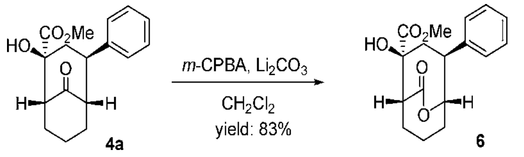
(12) (a) Wang, J.; Li, H.; Lou, B.; Zu, L.-S.; Guo, H.; Wang, W. *Chem. Eur. J.* **2006**, *12*, 4321. (b) Wang, J.; Li, H.; Zu, L.-S.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 425. (c) Zu, L.-S.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077. (d) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369. (e) Wang, W.; Li, H.; Wang, J. *Tetrahedron Lett.* **2005**, *46*, 5077. (f) Wang, W.; Li, H.; Wang, J.; Liao, L.-X. *Tetrahedron Lett.* **2004**, *45*, 8229. (g) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243.

(13) A trace amount of the corresponding Aldol product, Diels-Alder type product, and diastereoisomer of **4a** was observed in the reaction of **2a** and **3a**. These compounds were isolated by collection of all the byproducts of entries 1−13 in Table 1 and then purification by flash chromatography. For details, please see the Supporting Information.

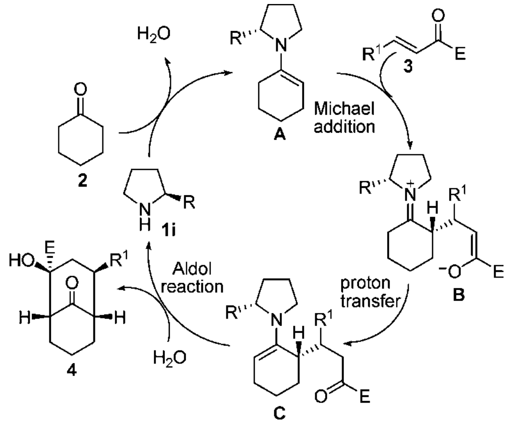
(14) For details, please see the Supporting Information.

in the presence of a catalytic amount of Li_2CO_3 (Scheme 3). Compound **6** was fully characterized by ^1H, ^{13}C NMR, and HRMS. The relative configuration has been determined by X-ray diffraction analysis on compound **6** (see the Supporting Information).

Scheme 3. The Conversion of Compound **4a** to Compound **6**



Scheme 4. A Proposed Mechanism for the Formal [3+3] Annulation Reaction



A proposed mechanism (as shown in Scheme 4) explains the present reaction. The ketone is transformed to the corresponding enamine **A** in the presence of catalyst **1i**. A Michael addition of **A** with enone **3**, followed by an isomerization and then an Aldol reaction affords the desired product **4** and regenerates the catalyst to finish a catalytic cycle.

On the basis of the experimental results described above, a stereochemical model was developed to account for the high enantioselectivity of the present reaction. As shown in Figure 2, catalyst **1i** was proposed as a bifunctional catalyst.

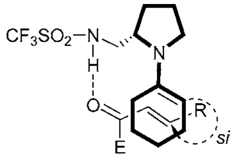


Figure 2. A possible stereochemical model.

The pyrrolidine reacts with cyclic ketone to form an enamine and the sulfonamide activates the enone via a hydrogen bond. The enamine attacked the enone from the si-face to afford the product, which was consistent with the experimental results.

In summary, we have developed an organocatalytic enantioselective formal [3+3] annulation reaction of cyclic ketones with enones, providing easy access to optically active 2-hydroxy-9-oxo-bicyclo[3.3.1]nonane derivatives with four stereocenters in one pot. The mild conditions, the high enantioselectivities, the good yields, and the [3.3.1] bicyclic skeleton[15] obtained make the current reaction potentially useful in organic synthesis. Further investigation of the scope of formal [3+3] cycloaddition and its application is underway.

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Supporting Information Available: Characterization data for all new compounds, CIF files for **4a**, **4g,** and **6**, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] (a) Cao, S.; Brodie, P. J.; Miller, J. S.; Ratovoson, F.; Birkinshaw, C.; Randrianasolo, S.; Rakotobe, E.; Rasamison, V. E.; Kingston, D. G. I. *J. Nat. Prod.* **2007**, *70*, 686 and references cited therein. (b) Hamed, W.; Brajeul, S.; Mahuteau-Betzer, F.; Thoison, O.; Mons, S.; Delpech, B.; Van Hung, N.; Se'venet, T.; Marazano, C. *J. Nat. Prod.* **2006**, *69*, 774 and references cited therein. (c) Baggett, S.; Protiva, P.; Mazzola, E. P.; Yang, H.; Ressler, E. T.; Basile, M. J.; Weinstein, I. B.; Kennelly, E. J. *J. Nat. Prod.* **2005**, *68*, 354 and references cited therein.