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Desulfonylative Methenylation of β-Keto Sulfones

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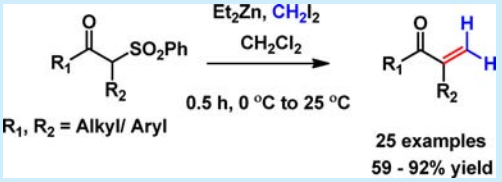
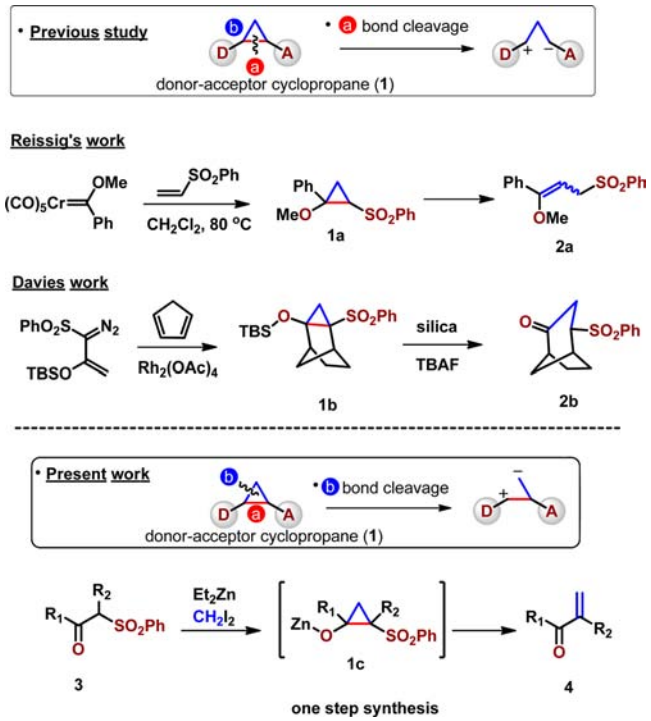
Supporting Information

ABSTRACT: A one-step strategy for the synthesis of α-methenyl ketones from β-keto sufones is reported. Success of the methodology is elaborated for the synthesis of chromanones and isoflavanones in one-step.



Donor−Acceptor (D−A) cyclopropanes serve as versatile building blocks in diverse chemical transformations, including cycloaddition, ring opening, and rearrangement reactions in organic synthesis.[1,2] It is established that D−A cyclopropanes **1** undergoes selective "a" bond cleavage (Scheme 1) due to polarization by the push−pull effect of donor and acceptor groups. In fact, this property has been very well exploited to synthesize enol ether **2a** by the selective "a" bond dissociation of **1a**.[3a]

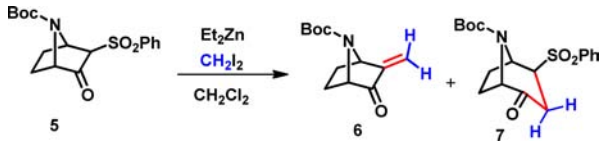
Scheme 1. Traditional and Developed Activation of D−A Cyclopropanes



Similarly, Davies et al. have also used this reaction to prepare γ-keto sulfone **2b** from the dissociation of **1b**, generated by cyclopropantion reaction of rhodium carbenoid with cyclopentadiene.[3b]

With this information in hand, we sought to prepare biologically active tropane alkaloids **7** by the cyclopropanation of the enolate of the optically pure **5**[4a] (0.1 M, CH_2Cl_2, 0 °C) using Furukawa-modified Simmons−Smith reagent [(Et_2Zn, (2 equiv), CH_2I_2 (2 equiv)], which gave a mixture of **6** and **7** (3:1) in 54% yield (Table 1, entry 2).[5]

Table 1. Optimization of Regioselective Bond Fragmentation of D−A Cyclopropane Intermediate



no.	equiv[a]	temp (°C)	time (min)	6:7[b]
1	2	−78	120	no reaction[c]
2	2	0	60	30:12
3	4	−78	120	no reaction[c]
4	4	0	45	50:22
5	4	0−25	30	72:0
6	4	30	5	20:0
7	6	0−25	10	48:0

[a]Equivalents of Et_2Zn and CH_2I_2 to 1 equiv of **5**. [b]Isolated yields. [c]Starting material recovered.

The formation of α-methenyl ketone **6**, however, was unexpected in this reaction. To obtain **7** as the major product, several experiments (Table 1) were performed; however, this remained elusive. It was surprising to note that reaction at 0−25 °C produced exclusively **6** in 72% isolated yield (Table 1, entry 5). Although this result was disappointing, we visualized its application in the preparation of the α-methenyl ketones from β-keto sulfones in one step. α-Methenyl ketones are important starting materials in cycloaddition,[6] Michael

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addition,[7] Morita–Baylis–Hillman reaction,[8] Nazarov cyclization,[9] and several catalytic transformation reactions.[10]

We report herein the successful transformation of a series of β-keto sulfones to α-methenyl ketones in one step by the reaction of diethylzinc in the presence of CH_2I_2.

Initially, to demonstrate this transformation, reaction of 2-phenylsulfonylacetophenone (**3a**) [4 equiv of Et_2Zn, 4 equiv of CH_2I_2, and 1 equiv of **3a** in 0.1 M CH_2Cl_2 at 0 °C] was performed, and acrylophenone (**4a**) (Figure 1) was obtained in

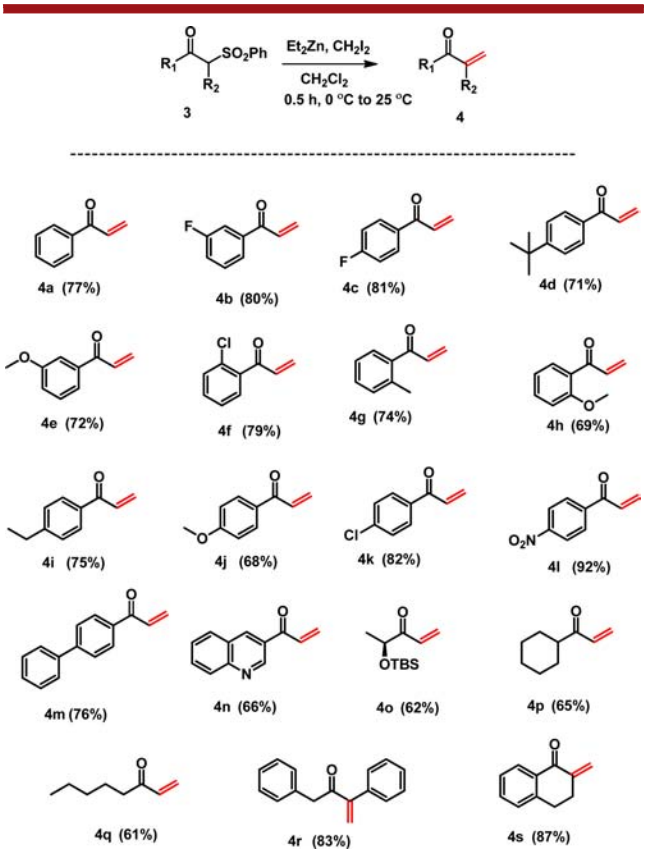


Figure 1. Example of the desulfonylative methenylation of β-keto sufones. (a) All of the reactions were carried out in the presence of 2 mmol of Et_2Zn and CH_2I_2 to 0.5 mmol of **3**. (b) Isolated yields.

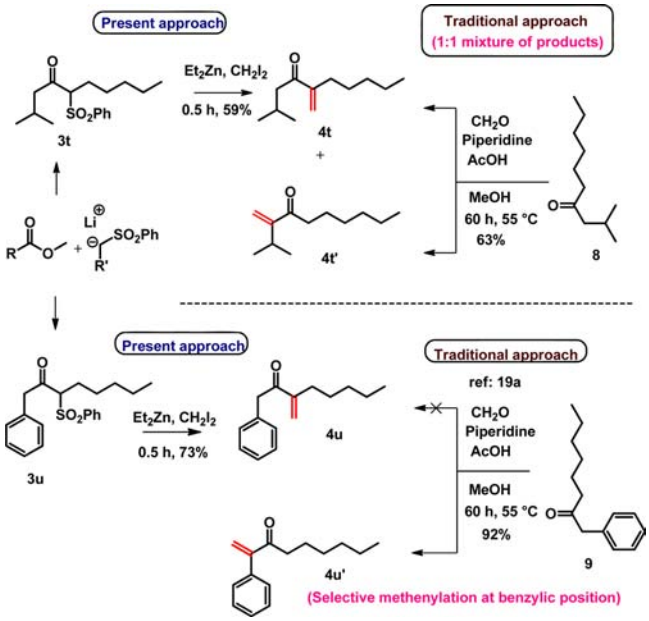
77% yield. This reaction can be used for gram-scale synthesis of α-methenyl ketones[11] with consistent yields. Usually, in Simmons–Smith reactions alkenes are starting materials for cyclopropanation;[12] however, in this reaction, formation of activated alkenes is observed. It may be noted that this is the first report of this kind where β-keto sulfones are easily transformed into α-methylene ketones. Previous reports show the transformation of β-keto sulfones to alkynyl,[13] alkenyl,[14] carbonyl,[15] and dicarbonyl[16] functionalities.

The generality of the reaction was established by carrying it out with a variety of β-keto sufones, and the results are shown in Figure 1. It is observed that all aromatic, heteroaromatic, and aliphatic β-keto sufones provided the corresponding α-methylene ketones in good yields (59–92%).

From Figure 1, it is clear that aromatic β-keto sufones provided higher yields compared to aliphatic β-keto sufones. Furthermore, it was noticed that aromatic β-keto sufones bearing electron-withdrawing substituents **4l** gave slightly higher yields than the electron-donating groups. This protocol is safely used for the transformation of enantiomerically pure **4o**, containing an acid-labile protecting group, without compromising the enantiomeric purity. Notably, α-sulfonyl aldehydes did not afford the desired acrolein derivatives under the optimized reaction conditions.

It may be worth emphasizing that, generally, α-methenyl ketones are prepared in three steps by a Mannich reaction–alkylation–elimination sequence with Eschenmoser's salt (dimethylmethylideneammonium iodide)[17] or a transiently formed methyleneammonium salt.[18] Although these approaches are elegant, regioselective α-methenylation of aliphatic ketones is a major limitation (Scheme 2).[19] For example, α-

Scheme 2. Traditional and Developed Method for α-Methenyl Ketones



methenylation of **8** is known to afford a 1:1 mixture of **4t** and **4t′** in 63% yield.[19] However, in our case, easily accessible β-keto sufone[20] **3t** under the present reaction conditions afforded **4t** exclusively. Furthermore, traditional α-methenylation of **9** proceeds selectively at a benzylic position to afford **4u′**;[19a] however, in the present case **4u** was formed in 73% yield.

Further application of this reaction was carried out by one-step transformation of **10a** to chromanone (**11a**) and **10b** to isoflavanones (**11b**) (Scheme 3) in moderate yields (54–58%). These compounds are shown to display a range of biological activity and have been shown to act as immunosuppressive agents,[21] possess antibacterial[22] and anticancer activity,[23] and act as α-glucosidase inhibitors.[24] Furthermore, **10c** is transformed to **11c** in two steps,[25] which is a precursor of bioactive sophorapterocarpan A.[26] Our attempt to synthesize dihydroquinolne **12** by identical reaction of **10d**, however, did not succeed.

On the basis of the above observations, a plausible reaction mechanism has been shown in Scheme 4.

It seems that reaction of **3** by zinc carbenoid or diethylzinc leads to **13**, which undergoes Simmons–Smith reaction to provide D–A cyclopropane **1c**. Subsequently, the leaving group ability[28] of the phenylsulfone group[4b] of activated D–A cyclopropane undergoes fragmentation to generate α,β-unsaturated ketone **4**. In order to support the mechanism, we have also analyzed the crude reaction mixture of **5** by mass

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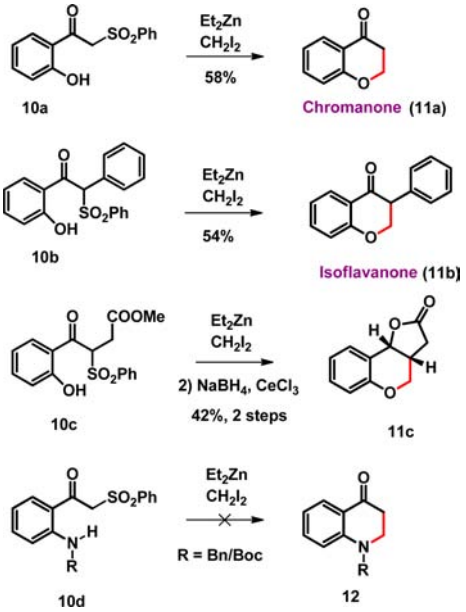
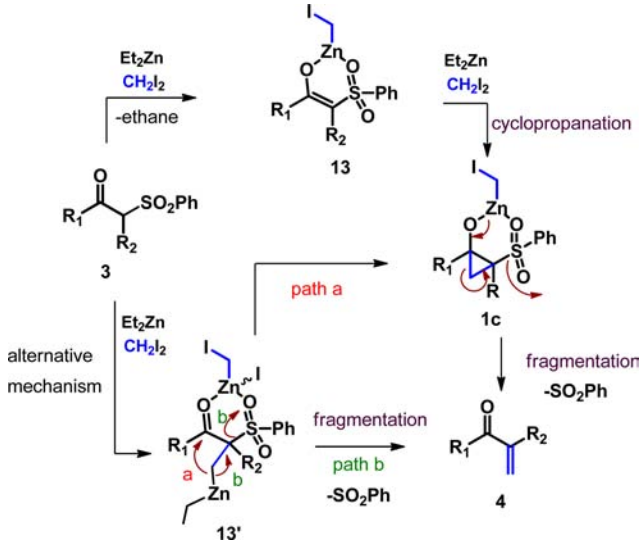
Scheme 3. Synthetic Applications of Desulfonylative Methenylation of β-Keto Sufones



Scheme 4. Plausible Mechanism for the Formation of α-Methenyl Ketones



spectrometry, which indicated the formation of $PhSO_2H$ by showing a mass of 164.9972 ($M + Na^+$). An alternative mechanism can also be possible via deprotonation of the active methelene proton by organozinc reagent to produce **13′** followed by fragmentation leading to the formation **4**. Reported experimental[5] and mechanistic investigations[27] for the zinc carbenoid insertion step further support both possibile proposed mechanisms.

In summary, a convenient protocol for the desulfonylative methenyaltion of β-keto sufones is described. The key feature of the method involves regioselective C−C bond fragmentation[29] of D−A cyclopropane followed by desulfonylation to give α-methenyl ketones. Further application of this method is demonstrated by preparing chromanones and isoflavanones in one step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02455.

Experimental procedures, compound characterization data, copies of NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For relevant reviews, see: (a) Reissig, H. U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) de Simone, F.; Waser, J. *Synthesis* **2009**, *2009*, 3353. (c) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (d) Campbell, M. J.; Johnson, J. S.; Parsons, A. T.; Pohlhaus, P. D.; Sanders, S. D. *J. Org. Chem.* **2010**, *75*, 6317. (e) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (f) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 5504. (g) Mel'nikov, M. Ya.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendeleev Commun.* **2011**, *21*, 293. (h) Novikov, R. A.; Tomilov, Yu. V. *Mendeleev Commun.* **2015**, *25*, 1. (i) de Nanteuil, F.; de Simone, F.; Frei, R.; Benfatti, F.; Serrano, E.; Waser, J. *Chem. Commun.* **2014**, *50*, 10912. (j) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804.

(2) Selected recent examples of D−A cyclopropane reactions: (a) Braun, C. M.; Congdon, E. A.; Nolin, K. A. *J. Org. Chem.* **2015**, *80*, 1979. (b) Rakhmankulov, E. R.; Ivanov, K. L.; Budynina, E. M.; Ivanova, O. A.; Chagarovskiy, A. O.; Skvortsov, D. A.; Latyshev, G. V.; Trushkov, I. V.; Melnikov, M. Ya. *Org. Lett.* **2015**, *17*, 770. (c) Kumar Pandey, A.; Ghosh, A.; Banerjee, P. *Eur. J. Org. Chem.* **2015**, *2015*, 2517. (d) Rivero, A. R.; Fernandez, I.; Ramirez de Arellano, C.; Sierra, M. A. *J. Org. Chem.* **2015**, *80*, 1207. (e) Zhu, J.; Liang, Y.; Wang, L.; Zheng, Z.-B.; Houk, K. N.; Tang, Y. *J. Am. Chem. Soc.* **2014**, *136*, 6900. (f) Zhang, H.-H.; Luo, Y.-C.; Wang, H.-P.; Chen, W.; Xu, P.-F. *Org. Lett.* **2014**, *16*, 4896. (g) Racine, S.; de Nanteuil, F.; Serrano, E.; Waser, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 8484. (h) Ghorai, M. K.; Talukdar, R.; Tiwari, D. P. *Org. Lett.* **2014**, *16*, 2204. (i) Wang, Z.; Ren, J.; Wang, Z. *Org. Lett.* **2013**, *15*, 5682. (j) Ivanov, K. L.; Villemson, E. V.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V.; Melnikov, M. Y. *Chem. - Eur. J.* **2015**, *21*, 4975. (k) Garve, L. K. B.; Barkawitz, P.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2014**, *16*, 5804.

(3) (a) Wienand, A.; Reissig, H.-U. *Tetrahedron Lett.* **1988**, *29*, 2315. (b) Davies, H. M. L.; Houser, J. H.; Thornley, C. *J. Org. Chem.* **1995**, *60*, 7529.

(4) (a) Pandey, G.; Tiwari, K. N.; Puranik, V. G. *Org. Lett.* **2008**, *10*, 3611. (b) Pandey, G.; Janakiram, V. *Chem. - Eur. J.* **2015**, *21*, 13120.

(5) (a) Brogan, J. B.; Zercher, C. K. *J. Org. Chem.* **1997**, *62*, 6444. (b) Hilgenkamp, R.; Zercher, C. K. *Tetrahedron* **2001**, *57*, 8793. (c) Verbicky, C. A.; Zercher, C. K. *J. Org. Chem.* **2000**, *65*, 5615.

(6) (a) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (b) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.

(7) For selected examples, see: (a) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448. (b) Trost, B. M.; Florez, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613. (c) Mann, R. K.; Parsons, J. G.; Rizzacasa, M. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1283.

DOI: 10.1021/acs.orglett.5b02455
Org. Lett. 2015, 17, 4890−4893

(8) For recent reviews, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614. (c) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511. (d) Shi, Y. L.; Shi, M. *Eur. J. Org. Chem.* **2007**, *2007*, 2905. (e) France, S.; Guerin, D. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.
(9) For reviews, see: (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1. (b) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, *1983*, 429.
(10) (a) Li, P.; Wen, S.; Yu, F.; Liu, Q.; Li, W.; Wang, Y.; Liang, X.; Ye, J. *Org. Lett.* **2009**, *11*, 753. (b) Northrup, A. B.; MacMillan, D. W. E. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (c) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504. (d) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108.
(11) 2-Phenylsulfonylacetophenone (**3a**) (3.0 g) afforded 1.5 g of acrylophenone (**4a**) in 77% yield (see the Supporting Information).
(12) (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (b) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041.
(13) (a) Lythgoe, B.; Waterhouse, I. *Tetrahedron Lett.* **1978**, *19*, 2625. (b) Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2429. (c) Bartlett, P. A.; Green, F. R., III; Rose, E. H. *J. Am. Chem. Soc.* **1978**, *100*, 4852. (d) Ihara, M.; Suzuki, S.; Taniguchi, T.; Tokunaga, Y.; Fukumoto, K. *Tetrahedron* **1995**, *51*, 9873.
(14) (a) Lugo, B. *Synlett* **1992**, 793. (b) Gamble, M. P.; Giblin, G. M. P.; Taylor, R. J. K. *Synlett* **1995**, *1995*, 779.
(15) (a) Caricato, G.; Savoia, D. *Synlett* **1994**, *1994*, 1015. (b) Pavri, N. P.; Trudell, M. L. *Tetrahedron Lett.* **1997**, *38*, 7993. (c) Jones, D. N.; Maybury, M. W. J.; Swallow, S.; Tomkinson, N. C. O. *Tetrahedron Lett.* **1993**, *34*, 8553. (d) Benedetti, F.; Berti, F.; Risaliti, A. *Tetrahedron Lett.* **1993**, *34*, 6443. (e) Kato, M.; Watanabe, M.; Vogler, B.; Awen, B. Z.; Masuda, Y.; Tooyama, Y.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 7071. (f) Santhosh, K. C.; Balasubramanian, K. K. *Tetrahedron Lett.* **1991**, *32*, 7727. (g) Hynes, J., Jr.; Overman, L. E.; Nasser, T.; Rucker, P. V. *Tetrahedron Lett.* **1998**, *39*, 4647.
(16) Williams, D. R.; Robinson, L. A.; Amato, G. S.; Osterhout, M. H. *J. Org. Chem.* **1992**, *57*, 3740.
(17) Kinast, G.; Tietze, L.-F. *Angew. Chem.* **1976**, *88*, 261.
(18) (a) Erkkila, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538. (b) Erkkila, A.; Pihko, P. M. *Eur. J. Org. Chem.* **2007**, *2007*, 4205.
(19) (a) Lange, J. H. M.; Attali, A.; Wals, H. C.; Mulder, A.; Zilaout, H.; Duursma, A.; Aken, H. H. M.; Vliet, B. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4992. (b) Shono, T.; Nishiguchi, I.; Komamura, T.; Sasaki, M. *J. Am. Chem. Soc.* **1979**, *101*, 984.
(20) Markitanov, Y. M.; Timoshenko, V. M.; Shermolovich, Y. G. *J. Sulfur Chem.* **2014**, *35*, 188.
(21) Shou, Q.-Y.; Fu, R.-Z.; Tan, Q.; Shen, Z.-W. *J. Agric. Food Chem.* **2009**, *57*, 6712.
(22) Tanaka, H.; Hattori, H.; Oh-Uchi, T.; Sato, M.; Sako, M.; Tateishi, Y.; Rizwani, G. H. *Nat. Prod. Res.* **2009**, *23*, 1089.
(23) Chin, Y.-W.; Mdee, L. K.; Mbwambo, Z. H.; Mi, Q.; Chai, H.-B.; Cragg, G. M.; Swanson, S. M.; Kinghorn, A. D. *J. Nat. Prod.* **2006**, *69*, 1649.
(24) Valentova, M.; Marek, R.; Svajdlenka, E.; Kubinova, R.; Suchy, V. *Fitoterapia* **2011**, *82*, 272.
(25) Santoso, H.; Casana, M. I.; Donner, C. D. *Org. Biomol. Chem.* **2014**, *12*, 171.
(26) Ozaki, Y.; Mochida, K.; Kim, S.-W. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1219.
(27) Eger, W. A.; Zercher, C. K.; Williams, C. M. *J. Org. Chem.* **2010**, *75*, 7322.
(28) (a) Beslin, J.; Vialle, J. *Tetrahedron* **1980**, *36*, 1943. (b) Liu, C.-H.; Wang, S.-H.; Ruszczycky, M. W.; Chen, H.; Li, K.; Murakami, K.; Liu, H.-W. *Org. Lett.* **2015**, *17*, 3342. (c) Kosobokov, M. D.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *Org. Lett.* **2015**, *17*, 760.
(29) Halskov, K. S.; Kniep, F.; Lauridsen, V. H.; Iversen, E. H.; Donslund, B. S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2015**, *137*, 1685.

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