JOC Article
pubs.acs.org/joc

A Ring Contraction Strategy toward a Diastereoselective Total Synthesis of (+)-Bakkenolide A

Vânia M. T. Carneiro, Helena M. C. Ferraz,† Tiago O. Vieira, Eloisa E. Ishikawa, and Luiz F. Silva, Jr.*

Instituto de Química, Universidade de São Paulo, Av. Prof. Lineu Prestes, 748, CP 26077, CEP 05513-970 São Paulo SP, Brazil. †Deceased.

luizfsjr@iq.usp.br

Received January 22, 2010

A diastereoselective route to (+)-bakkenolide A is presented from the readily available optically active Wieland−Miescher ketone. This novel synthesis of this sesquiterpene lactone features the following as key stereoselective transformations: (i) the ring contraction reaction of a octalone mediated by thallium(III) nitrate (TTN); (ii) a hydrogenation to create the cis-fused junction; and (iii) the formation of the C7 quaternary center through an enolate intermediate. Furthermore, during this work, the absolute configuration of a trinorsesquiterpene isolated from *Senecio Humillimus* was assigned.

Introduction

The most famous member of the bakkanes class of natural products is (+)-bakkenolide A, (+)-**1** (Figure 1), which was first isolated in the late 60′s.[1] This sesquiterpene lactone displays cytotoxic activity against several cells lines, as well as insect antifeedant activity.[2] Several routes have been developed for the synthesis of bakkanes,[3] including for bakkenolide A.[4] Among them, the comprehensive work of Greene and his group must be highlighted.[5] However,

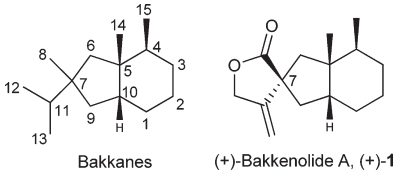


FIGURE 1. Bakkane skeleton and structure of (+)-bakkenolide A.

in their 11-step route for (+)-bakkenolide A,[4d,h] the C7 quaternary carbon was not formed diastereoselectively and, eventually, (+)-**1** was obtained together with its C-7 epimer in a 3:1 mixture, respectively. Indeed, this is a key issue in the synthesis of bakkanes and low diastereoselective

(1) (a) Naya, K.; Takagi, I.; Hayashi, M.; Nakamura, S.; Kobayashi, M.; Katsumura, S. *Chem. Ind.* **1968**, 318. (b) Abe, N.; Onoda, R.; Shirahata, K.; Kato, T.; Woods, M. C.; Kitahara, Y. *Tetrahedron Lett.* **1968**, 369.

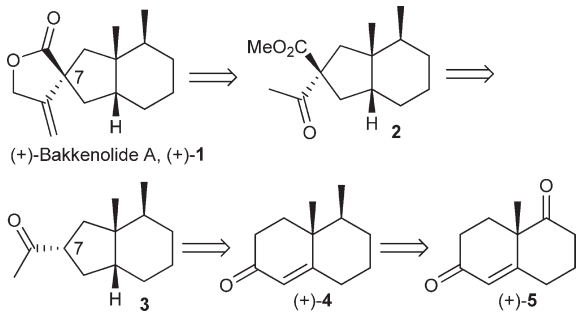
(2) (a) Jamieson, G. R.; Reid, E. H.; Turner, B. P.; Jamieson, A. T. *Phytochemistry* **1976**, *15*, 1713. (b) Kano, K.; Hayashi, K.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1982**, *30*, 1198. (c) Nawrot, J.; Bloszyk, E.; Harmatha, J.; Novotný, L. *J. Appl. Entomol.* **1984**, *98*, 394. (d) Nawrot, J.; Harmatha, J.; Novotný, L. *Biochem. Syst. Ecol.* **1984**, *12*, 99. (e) Nawrot, J.; Bloszyk, E.; Harmatha, J.; Novotný, L.; Drozdz, B. *Acta Entomol. Bohemoslov.* **1986**, *83*, 327. (f) Kreckova, J.; Krecek, J.; Harmatha, J. *Pr. Nauk. Inst. Chem. Org. Fiz. Politech. Wroclaw.* **1988**, *33*, 105. (g) Rosinski, R.; Bloszyk, E.; Harmatha, J.; Knapik, A. *Pr. Nauk. Inst. Chem. Org. Fiz. Politech. Wroclaw.* **1988**, *33*, 91. (h) Nawrot, J.; Koul, O.; Isman, M. B.; Harmatha, J. *J. Appl. Entomol.* **1991**, *112*, 194. (i) Harmatha, J.; Nawrot, J. *Biochem. Syst. Ecol.* **1984**, *12*, 95. (j) Li, E.-W.; Gao, K.; Jia, Z.-J. *Pharmazie* **2004**, *59*, 646.

(3) For a review, see: (a) Silva, L. F., Jr. *Synthesis* **2001**, 671. For an account, see: (b) Brocksom, T. J.; Brocksom, U.; Constantino, M. G. *Quim. Nova* **2008**, *31*, 937. For some papers concerning the synthesis of bakkanes, see: (c) Jiang, C.-H.; Bhattacharyya, A.; Sha, C.-K. *Org. Lett.* **2007**, *9*, 3241. (d) Srikrishna, A.; Reddy, T. J. *Arkivoc* **2001**, 9. (e) Srikrishna, A.; Nagaraju, S.; Venkateswarlu, S.; Hiremath, U. S.; Reddy, T. J.; Venugopalan, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2069.

(4) Syntheses of bakkenolide A: (a) Evans, D. A.; Sims, C. L. *Tetrahedron Lett.* **1973**, 4691. (b) Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, *99*, 5453. (c) Greene, A. E.; Deprés, J.-P.; Coelho, F.; Brocksom, T. J. *J. Org. Chem.* **1985**, *50*, 3943. (d) Greene, A. E.; Coelho, F.; Deprés, J.-P.; Brocksom, T. J. *Tetrahedron Lett.* **1988**, *29*, 5661. (e) Srikrishna, A.; Reddy, T. J.; Nagaraju, S.; Sattigeri, J. A. *Tetrahedron Lett.* **1994**, *35*, 7841. (f) Back, T. G.; Payne, J. E. *Org. Lett.* **1999**, *1*, 663. (g) Back, T. G.; Nava-Salgado, V. O.; Payne, J. E. *J. Org. Chem.* **2001**, *66*, 4361. (h) Brocksom, T. J.; Coelho, F.; Deprés, J.-P.; Greene, A. E.; de Lima, M. E. F.; Hamelin, O.; Hartmann, B.; Kanazawa, A. M.; Wang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15313. (i) Reddy, D. S.; Kozmin, S. A. *J. Org. Chem.* **2004**, *69*, 4860. (j) Reddy, D. S. *Org. Lett.* **2004**, *6*, 3345. (k) Constantino, M. G.; de Oliveira, K. T.; Polo, E. C.; da Silva, G. V. J.; Brocksom, T. J. *J. Org. Chem.* **2006**, *71*, 9880. (l) Kato, K.; Motodate, S.; Takaishi, S.; Kusakabe, T.; Akita, H. *Tetrahedron.* **2008**, *64*, 4627. (m) Kusakabe, T.; Kato, K.; Motodate, S.; Takaishi, S.; Akita, H. *Chem. Pharm. Bull.* **2008**, *56*, 1436. (n) Maity, S.; Ghosh, S. *Tetrahedron* **2009**, *65*, 9202.

DOI: 10.1021/jo100108b Published on Web 04/08/2010

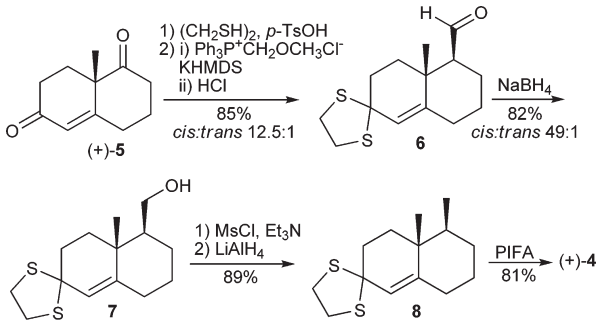
SCHEME 1. Ring Contraction Route for (+)-Bakkenolide A



in the creation of the carbon that originates the spiro lactone moiety can also be noted in racemic syntheses of bakkenolide A.[4c,f,g,k] Another approach to obtain (+)-**1** was recently developed by Kato and co-workers.[4l,m] In their 13-step synthesis from 2-methyl-1,3-cyclohexanedione, the required optically active intermediate was obtained in 22% yield and in 95% of enantiomeric excess, through a kinetic resolution. In this scenario, we herein described a new and diastereoselective route to (+)-bakkenolide A.

We envisioned that (+)-**1** could be synthesized from the keto-ester **2** by α-oxidation of the carbonyl group followed by lactonization. The keto-ester **2** would be obtained from the ketone **3** through the acylation of an enolate intermediate. Finally, the ketone **3** would be obtained by the oxidative rearrangement of the optically active octalone **4**, followed by diastereoselective hydrogenation and functional group transformations. Thallium(III) and iodine(III) reagents could a priori be used in such a rearrangement.[6] There are no precedents for the ring contraction of octalones using I(III). Regarding Tl(III), ring contraction product was obtained using thallium(III) nitrate (TTN) in a mixture of trimethylorthoformate (TMOF) and MeOH.[7a] On the other hand, dehydrogenation is observed after treatment with thallium(III) acetate (TTA) in acetic acid.[7b] The oxidation of octalone **4** with thallium(III) has not been investigated in these papers. The preparation of (+)-**4** has been described from the readily available Wieland−Miescher ketone (+)-**5** (Scheme 1). Several protocols have been developed for the preparation of (+)-**5** in optically pure form.[8] Furthermore, ketone (+)-**5** and its enantiomer are commercially available.

SCHEME 2. Preparation of the Octalone (+)-4



Results and Discussion

The starting Wieland−Mischer ketone (+)-**5** was obtained in large amounts and in high enantiomeric excess from methyl vinyl ketone and 2-methylcyclohexane-1,3-dione through Robinson annulation catalyzed by 5 mol % of *S*-proline.[8a,b] The octalone (+)-**4** was prepared from (+)-**5**, as described by Paquette and co-workers,[9] although their route was modified in some steps (Scheme 2). The main alteration was the use of the iodine(III) reagent $PhI(OCOCF_3)_2$ (PIFA) instead of TTN to perform the deprotection of the thioketal group of **8**.[10] Additionally, the reduction of the mesylate was performed with $LiAlH_4$ in the place of Super-Hydride ($LiBHEt_3$). Other small modifications are described in the Supporting Information. Racemic **4** was also prepared for testing the key ring contraction step. Two different routes were used.[11] The protocol of Zoretic and co-workers gave (±)-**4** in two steps, although the product was obtained together with its epimer in 9:1 ratio.[11a] An adaptation of routes described in the literature[11b,c] gave (±)-**4** as a single diastereomer, but in several steps (see the Supporting Information).

With the octalone **4** in hand, we start to investigate the rearrangement step using iodine(III) or thallium(III). The expected products of this ring contraction (**9**/**10**) bear a double bond and, consequently, are also prone to react with electrophilic species, such as thallium(III) and iodine(III). This constitutes one of the challenges of this transformation. Several conditions were tested with (+)- and/or (±)-**4** and we summarize the main results in the following paragraphs. The reaction of **4** with iodine(III) was tested with [hydroxy(tosyloxy)iodo]benzene (HTIB) (Koser's reagent), with diacetoxyiodobenzene (DIB), and with PIFA (Table 1). A mixture of several compounds was obtained under all conditions, except in the cases shown in entries 1 and 7, where no reaction was observed. The best yield (40%) for the ring contraction products (**9**/**10**) was obtained by using DIB in TMOF:MeOH

(5) (a) Coelho, F.; Deprés, J.-P.; Brocksom, T. J.; Greene, A. E. *Tetrahedron Lett*. **1989**, *30*, 565. (b) Hartmann, B.; Kanazawa, A. M.; Deprés, J.-P.; Greene, A. E. *Tetrahedron Lett*. **1991**, *32*, 767. (c) Hartmann, B.; Deprés, J.-P.; Greene, A. E.; de Lima, M. E. F. *Tetrahedron Lett*. **1993**, *34*, 1487. (d) Hamelin, O.; Deprés, J.-P.; Greene, A. E.; Tinant, B.; Declercq, J.-P. *J. Am. Chem. Soc*. **1996**, *118*, 9992. (e) Hamelin, O.; Deprés, J.-P.; Heidenhain, S.; Greene, A. E. *Nat. Prod. Lett*. **1997**, *10*, 99. (f) Hamelin, O.; Wang, Y.; Deprés, J.-P.; Greene, A. E. *Angew. Chem., Int. Ed*. **2000**, *39*, 4314. (g) Hartmann, B.; Kanazawa, A. M.; Deprés, J.-P.; Greene, A. E. *Tetrahedron Lett*. **1993**, *34*, 3875. (h) See also refs 4c, 4d, and 4h.

(6) For reviews concerning ring contraction reactions, see: (a) Redmore, D.; Gutsche, C. D. In *Advances in Alicyclic Chemistry*; Hart, H., Karabastos, G. J., Eds.; Academic Press: New York , 1971; Vol. 3, p 1. (b) Silva, L. F., Jr. *Tetrahedron* **2002**, *58*, 9137. For a review concerning Tl(III)-mediated ring contractions, see: (c) Ferraz, H. M. C.; Silva, L. F., Jr. *Quim. Nova* **2000**, *23*, 216. See also: (d) Silva, L. F., Jr.; Carneiro, V. M. T. *Synthesis* **2010**, 1059. For a review concerning I(III)-mediated ring contractions, see: (e) Silva, L. F., Jr. *Molecules* **2006**, *11*, 421.

(7) (a) Mincione, E.; Bovicelli, P.; Gil, J. B.; Forcellese, M. L. *Gazz. Chim. Ital*. **1985**, *115*, 37. (b) Banerjee, A. K.; Carrasco, M. C.; Peña-Matheud, C. A. *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 94.

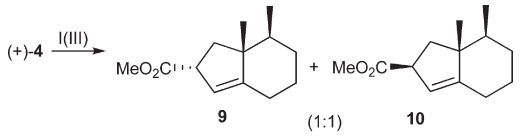
(8) The procedure of the following papers was used in this work: (a) Barrack, S. A.; Okamura, W. H. *J. Org. Chem*. **1986**, *51*, 3201. (b) Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Org. Synth*. **1985**, *63*, 37. For other selected recents papers, see: (c) Bui, T.; Barbas, C. F., III *Tetrahedron Lett*. **2000**, *41*, 6951. (d) Kriis, K.; Kanger, T.; Laars, M.; Kailas, T.; Muurisepp, A.-M.; Pehk, T.; Lopp, M. *Synlett* **2006**, 1699. (e) Akahara, Y.; Inage, N.; Nagamine., T.; Inomata, K.; Endo, Y. *Heterocycles* **2007**, *74*, 637. (f) Arriba, A. L. F.; Simón, L.; Raposo, C.; Alcázar, V.; Morán, J. R. *Tetrahedron* **2009**, *65*, 4841. (g) Almasi, D.; Alonso, D. A.; Balaguer, A.-N.; Nájera, C. *Adv. Synth. Catal*. **2009**, *351*, 1123. (h) Akahane, Y.; Inomata, K.; Endo, Y. *Heterocycles* **2009**, *77*, 1065.

(9) Paquette, L. A.; Wang, T.-Z.; Phillippo, C. M. G.; Wang, S. *J. Am. Chem. Soc*. **1994**, *116*, 3367.

(10) Stork, G.; Zhao, K. *Tetrahedron Lett*. **1989**, *30*, 287.

(11) (a) Zoretic, P. A.; Golen, J. A.; Saltzman, M. D. *J. Org. Chem*. **1981**, *46*, 3554. (b) Piers, E.; Britton, R. W.; de Waal, W. *Can. J. Chem*. **1969**, *47*, 4307. (c) Cuesta, X.; González, A.; Bonjoch, J. *Tetrahedron: Asymmetry* **1999**, *10*, 3365.

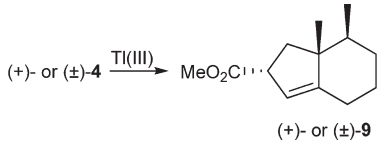
TABLE 1. Oxidation of Octalone 4 with Iodine(III)



entry	conditions	product (isolated yield)
1	HTIB, MeCN, rt, 24 h[a]	no reaction
2	HTIB, TMOF, 0 °C, 1 min[a]	**9**/**10** (GC: 6%)
3	DIB, TMOF, 10% $HClO_4$, rt, 20 h[b]	**9**/**10** (10%)
4	PIFA, TMOF, 10% $HClO_4$, rt, 30 min[c]	**9**/**10** (GC: 8%)
5	DIB, TMOF, *p*-TsOH, rt, 1 min[d]	complex mixture
6	DIB, TMOF, *p*-TsOH, 0 °C to rt, 2 h[d]	**9**/**10** (28%)
7	DIB, TMOF:MeOH (7:3), rt, 4 days[c,e]	no reaction
8	DIB, TMOF:MeOH (7:3), HNO_3, rt, 17.5 h[d,e]	**9**/**10** (40%)
9	DIB, TMOF:MeOH (7:3), *p*-TsOH, rt, 1 h[d,e]	**9**/**10** (36%)

[a]1 equiv of HTIB. [b]1.2 equiv of DIB. [c]2 equiv of I(III) reagent. [d]2 equiv of DIB and 1 equiv of acid. [e]Total volume of solvent: 20 mL/1 mmol, whereas in other conditions 7 mL/1 mmol was used.

TABLE 2. Oxidation of Octalone 4 with 1.1 equiv of TTN



entry	conditions	product (isolated yield)
1	TMOF:MeOH (4:3), 0 °C, 30 min	(+)-**9** (48%)[a]
2	TMOF, 0 °C, 15 min	(+)-**9** (36−40%)[b]
3	MeCN:MeOH:TMOF (1:1:1), rt, 10 min	(+)-**9** (38%)[b]
4	TMOF:TFE[c] (1:1), 0 °C, 5 min	(±)-**9** (15%)[b]
5	TMOF:MeOH (4:3), 0 °C, 15 min 7 mL/1 mmol	(+)-**9** (36−38%)
6	TMOF:MeOH (7:3), 0 °C, 15 min 10 mL/1 mmol	(±)-**9** (51%)
7	TMOF:MeOH (7:3), rt, 5 min 10 mL/1 mmol	(±)-**9** (52%)
8	TMOF:MeOH (7:3), rt, 10 min 20 mL/1 mmol	(±)-**9** (59%)
9	TMOF:MeOH (7:3), rt, 30 min 40 mL/1 mmol	(±)-**9** (58%)
10	TMOF:MeOH (7:3), rt, 10 min 20 mL/1 mmol	(+)-**9** (59%)

[a]Total volume of solvent: 12 mL/1 mmol; 1.2 equiv of TTN. [b]Total volume of solvent: 7 mL/1 mmol. [c]TFE: 2,2,2-trifluoroethanol.

(7:3), in the presence of HNO_3, with a total volume of solvent of 20 mL for each mmol of substrate (entry 8).

The reaction of **4** with thallium(III) was also studied. On the basis of previous work[7] and on our experience,[6b−d] we focus the attempts on TTN. By using the conditions described by Mincione et al.,[7a] the desired hydrindene **9** was obtained in 48% yield (Table 2, entry 1). Several other conditions were then tried with use of TTN, but the yield of **9** did not improved (entries 2−5).[12] By increasing the amount of solvent from 7 mL/1 mmol to 10 mL and the proportion of TMOF to MeOH, the racemic product **9** was isolated in 51% yield (entry 6). Reduction on reaction time was achieved by increasing the temperature, without significantly altering the yield (entries 6 and 7). Finally, the effect of dilution was investigated for (±)-**4** (entries 7−9). A more diluted condition could favor the intramolecular

(12) No reaction was observed with the following conditions: MeOH:THF (2:1), H_2O cat., rt, 4 h; MeCN, rt, 3 h; MeCN:MeOH (1:1), rt, 1 h; CH_2Cl_2, rt. Employing $HClO_4$ as solvent, a complex mixture of products was formed.

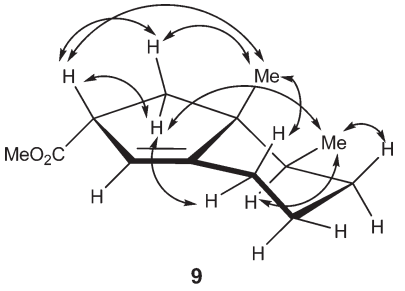
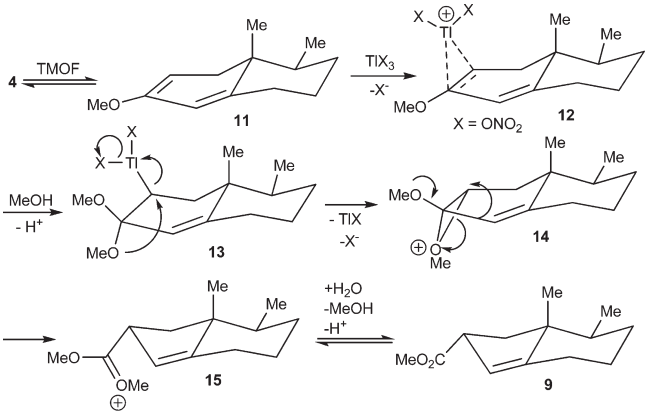


FIGURE 2. NOE cross-peaks of ring contraction product **9**.

SCHEME 3. Mechanism for the Ring Contraction of Octalones



rearrangement toward other intermolecular oxidations and, thus, increase the yield of **9**. Indeed, by using 20 mL of solvent for each mmol of substrate, the ring contraction product **9** was isolated in 59% yield (entry 8), whereas in 10 mL the yield was 52% (entry 7). Increasing the amount further to 40 mL did not lead to a better result (entry 9). Then, the condition with 20 mL/1 mmol was applied to (+)-**4**, giving an analogous yield, as expected (entry 10).

The ring contraction mediated by thallium(III) led to **9**, as a single diastereomer. The relative configuration of C7 in this compound was assessed by means of 2D COSY, 2D HETCOR and 2D NOESY. Figure 2 shows the most important NOE cross-peaks.

The suggested mechanism can explain the observed diastereoselectivity.[13] The first step would be the attack of Tl(III) to the enol ether **11** giving the thallonium ion **12**. The trans-diaxial ring-opening of this onium ion by the methanol led to the organothallium intermediate **13**. The exit of thallium(I) would occur by the intramolecular attack of the methoxyl oxygen, giving the oxonium-like ion **14**, on which the rearrangement would take place delivering the ring contraction product **9** (Scheme 3). The ring contraction mediated by iodine(III) would occur by an analogous mechanism. However, the acidic medium would promote the epimerization and a mixture of diastereomers was isolated (Table 1).

The ring contraction step was tested by using enol ether **16** as the substrate, which was prepared from (+)-(*S*,*S*)-**4**.[14]

(13) (a) McKillop, A.; Hunt, J. D.; Taylor, E. C. *J. Org. Chem.* **1972**, *37*, 3381. (b) Ferraz, H. M. C.; Silva, L. F., Jr. *Tetrahedron Lett.* **1997**, *38*, 1899. (c) Ferraz, H. M. C.; Silva, L. F., Jr. *J. Org. Chem.* **1998**, *63*, 1716. (d) Ferraz, H. M. C.; Silva, L. F., Jr. *J. Braz. Chem. Soc.* **2001**, *12*, 548.

(14) (a) Govindan, S. V.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 2593. (b) Tanabe, M.; Crowe, D. F. *J. Chem. Soc., Chem. Commun.* **1973**, *16*, 564.

SCHEME 4. Synthesis of the Trinorsesquiterpene 17

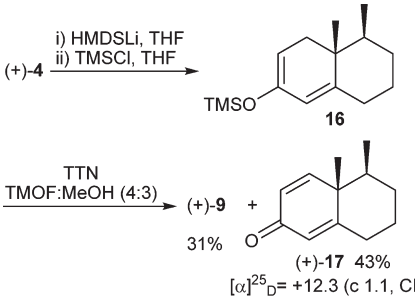
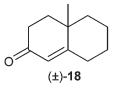
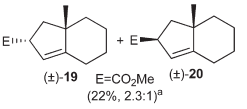
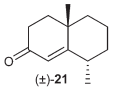
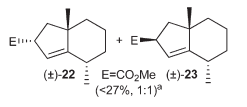


TABLE 3. Oxidation of Octalones 18 and 21 with I(III) or with Tl(III)

Entry	Substrate	Conditions	Product (Isolated Yield)
1	 (±)-**18**	DIB, TMOF, *p*-TsOH, -40 to 0 °C, 3.5 h	 (±)-**19** E=CO_2Me (±)-**20** (22%, 2.3:1)[a]
2	 (±)-**21**	DIB, TMOF, *p*-TsOH, 0 °C, 4 h	 (±)-**22** E=CO_2Me (±)-**23** (<27%, 1:1)[a]
3	(±)-**18**	TTN, TMOF/MeOH (7:3), rt, 10 min	(±)-**19** (14%)[b]
4	(±)-**21**	TTN, TMOF/MeOH (7:3), rt, 10 min	(±)-**22** (32-48%)[c]
5	(±)-**18**	TTN, TMOF/MeOH (4:3), 0 ºC, 30 min	Mincione et al.[7a]: (±)-**19** (44%)[b]
6	(±)-**21**	TTN, TMOF/MeOH (4:3), 0 ºC, 30 min	Mincione et al.[7a]: (±)-**22** (61%)[b]

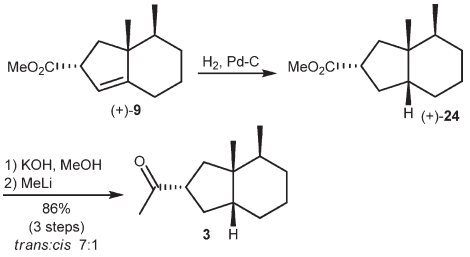
[a] 2 equiv of DIB and 1 equiv of *p*-TsOH. [b] 1.2 equiv of $Tl(NO_3)_3 \cdot 3H_2O$. [c] 1.1 equiv of $Tl(NO_3)_3 \cdot 3H_2O$.

When **16** was treated with TTN, the hydrindene (+)-**9** was isolated as the minor component. The major product was the dienone (+)-(*S*,*S*)-**17** (Scheme 4). The dienone **17** is a trinorsesquiterpene that was isolated from *Senecio Humillimus*, as the levorotatory enantiomer $[\alpha]^{24}_D$ −12.4 (*c* 1.0, $CHCl_3$).[15] On the basis of the absolute configuration of related natural products and on biosynthetic considerations, Bohlmann suggested the absolute configuration of **17** as (*S*,*S*).[15] However, in conclusion, on the basis of our results the absolute configuration of (−)-**17** is (*R*,*R*).

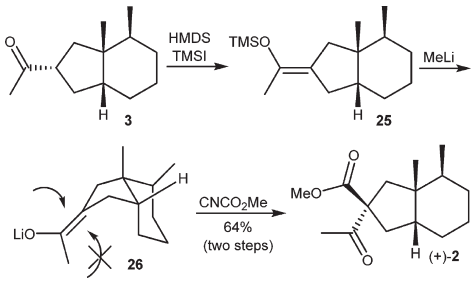
The oxidation of other octalones, namely **18** and **21**, was also investigated with iodine(III) and thallium(III) under several conditions. Representative results are herein discussed. The reaction of enone **18** with DIB led to the ring contraction products **19** and **20** as a 2.3:1 mixture, respectively, in 22% yield (Table 3, entry 1). Under similar conditions, the octalone **21** gave **22** and **23**, together with other unidentified compounds in a total yield of 27% (entry 2). The conditions optimized by us for the thallium(III)-mediated ring contraction of **4** (entry 8, Table 2) are better than those reported by Mincione et al.[7a] (entry 1, Table 2). On the other hand, for the octalones **18** and **21**, the protocol of Mincione is more efficient (compare entries 3 and 5, and 4 and 6 of Table 3).

(15) Bohlmann, F.; Kramp, W.; Robinson, H.; King, R. M. *Phytochemistry* **1981**, *20*, 1739.

SCHEME 5. Synthesis of the *cis*-Hydrindane 3



SCHEME 6. Creation of the C7 Quaternary Center



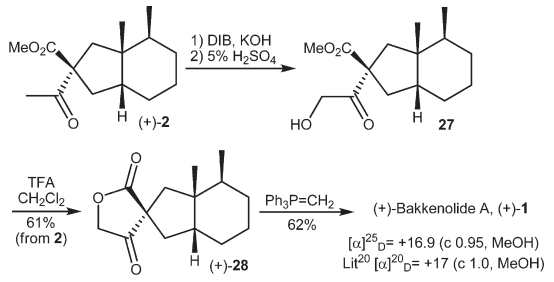
After a detailed study of the ring contraction step, the total synthesis was continued. The unsaturated ester **9** was hydrogenated giving the required *cis*-hydrindane (+)-**24**. The formation of the corresponding compound with a trans junction was not observed in the crude product. The chemical shift of the methyl group at C3a can be used to assign the ring junction as cis or trans in hydrindanes, as **24**. For the trans diastereomer, the chemical shift would be around 0.7 ppm, whereas for the corresponding cis it would be at ca. 1.0 ppm.[13c,d] The high selectivity can be explained by the delivery of the hydrogen to the less hindered convex face, where the CO_2Me group may have an influence. The ester **24** was then hydrolyzed and the carboxylic acid treated with MeLi,[16] leading to the corresponding ketone **3**, in 86% yield from **9** (Scheme 5). The basic conditions led to a partial epimerization of C7, which is not important at this stage, because the next step would involve the formation of the enolate of the ketone **3**.

Exposing the *cis*-hydrindane **3** to HMDS and TMSI led to the thermodynamic enol ether **25**, which was treated with MeLi delivering the enolate **26**. This enolate reacted with $CNCO_2Me$ only by the convex face giving the keto-ester **2**, as a single diastereomer (Scheme 6).[4j,17]

After the diastereoselective creation of the C7 quaternary center, the formation of the spiro lactone moiety would be required to accomplish the total synthesis of **1**. Among many options, we decided to perform the α-oxidation of (+)-**2** using hypervalent iodine.[18] Indeed, treatment of **2** with DIB gave the α-hydroxyketone **27**.[18c] Subsequent TFA-catalyzed lactonization furnished the keto-lactone **28**, in 61% yield

(16) Adcock, W.; Abeywickrema, A. N. *J. Org. Chem.* **1982**, *47*, 2951.
(17) (a) Mori, K.; Matsushima, Y. *Synthesis* **1995**, 845. (b) Ferraz, H. M. C.; Vieira, T. O.; Silva, L. F., Jr. *Synthesis* **2006**, 2748.
(18) (a) Moriarty, R. M.; Prakash, O. *Org. React.* **1999**, *54*, 273. (b) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (c) Moriarty, R. M.; Berglund, B. A.; Penmasta, R. *Tetrahedron Lett.* **1992**, *33*, 6065. (d) See also, ref 6e.

SCHEME 7. Formation of the Spiro Lactone Moiety



from **2**.[19] Finally, Wittig olefination of **28** led to (+)-bakkenolide A (+)-(**1**), in 62% yield (Scheme 7). The analytical data of our sample of **1** are equivalent to those previously reported.[4i,20]

Conclusion

In summary, a novel total synthesis of (+)-bakkenolide A (+)-**1** was accomplished in 15 steps and in 6% yield from the readily available Wieland−Miescher ketone (+)-(**5**), which can be prepared in large amounts by an organocatalytic reaction. This stereoselective synthesis features the following as key steps: (i) the ring contraction reaction of the octalone **4**; (ii) a stereoselective hydrogenation to create the required cis-fused junction; and (iii) the diastereoselective formation of the C7 quaternary center through the enolate **26**. Moreover, the absolute configuration of the trinorsesquiterpene (−)-**17**, which was isolated from *Senecio Humillimus*, was assigned as (*R*,*R*).

Experimental Section

(2*R*,7*S*,7a*R*)-Methyl 1,2,4,5,6,7,7a-Heptahydro-7,7a-dimethyl-2*H*-indene-2-carboxylate, (+)-9. To a stirred solution of $Tl(NO_3)_3 \cdot 3H_2O$ (0.488 g, 1.1 mmol) in TMOF (6 mL) and in MeOH (6 mL), stirred for 10 min, was added the octalone (+)-**4** (0.179 g, 1.0 mmol) in TMOF (8 mL) at rt. After 2 min an abundant precipitation was observed and the reaction mixture was stirred for 10 min at rt. The resulting suspension was filtered through a silica gel pad (ca. 10 cm), using CH_2Cl_2 (100 mL) as eluent. The filtrate was washed with a saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL) and dried over anhyd $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes:Et_2O, 9:1 as eluent) immediately after concentration of the solvent, to give (+)-**9** (59%, 0.123 g, 0.591 mmol) as a light yellow oil. R_f 0.70 (10% AcOEt/hexanes); IR (film) 2956, 2931, 2859, 1740, 1436, 1201, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, d, J = 6.6 Hz), 0.91 (3H, s), 1.19−1.48 (4H, m), 1.71−1.79 (1H, m), 1.87 (1H, dd, J = 12.8 and 9.0 Hz), 1.90−2.09 (1H, m), 2.04 (1H, dd, J = 12.8 and 8.1 Hz), 2.26−2.33 (1H, m), 3.54 (1H, ddt, J = 8.67, 4.01, and 1.78 Hz), 3.69 (3H, s), 5.17 (t, J = 1.9, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 16.9, 25.8, 26.7, 30.3, 42.9, 44.0, 47.5, 49.6, 51.7, 117.0, 153.7, 176.1; LRMS m/z (%) 208 ($M^{+\bullet}$, 19), 149 (100), 148 (51), 133 (29), 93 (66), 91 (40); HRMS m/z $C_{13}H_{20}O_2$ $(M + H)^+$ calcd 209.1536, found 209.1535; $[\alpha]^{25}_D$ +56.2 (c 1.0, $CHCl_3$).

(2*S*,3a*R*,4*S*,7a*R*)-Methyl Octahydro-3a,4-dimethyl-1*H*-indene-2-carboxylate, (+)-24. An autoclave charged with (+)-**9** (0.175 g, 0.841 mmol), 10% (w/w) Pd/C (0.009 g, 5% w/w), and anhyd MeOH (2.7 mL) was purged 3 times with H_2. The autoclave was charged with 2.5 atm of H_2. The reaction mixture was stirred for 3.5 h, when the mixture was filtered with Et_2O (30 mL) as eluent. The organic phase was dried over anhyd $MgSO_4$. The solvent was removed under reduced pressure to give (+)-**24** (0.166 g) as a colorless oil, which was used in the next step without purification. R_f 0.70 (10% AcOEt/hexanes); IR (film) 2958, 2927, 2865, 1737, 1199, 1172 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.79 (3H, d, J = 7.0 Hz), 0.88 (3H, s), 1.06−1.16 (1H, m), 1.37−1.60 (7H, m), 1.67−1.73 (1H, m), 1.79−1.85 (1H, m), 2.05−2.13 (2H, m), 2.85 (1H, dddd, J = 5.3, 8.8, 9.5, and 11.4 Hz), 3.67 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.4, 19.9, 21.1, 24.2, 30.7, 32.8, 33.7, 40.6, 41.6, 43.0, 47.3, 51.6, 177.7; LRMS m/z (%) 210 ($M^{+\bullet}$, 11%), 178 (59), 151 (48), 109 (45), 95 (65), 81 (100), 41 (62); HRMS m/z $C_{13}H_{22}O_2$ $(M + H)^+$ calcd 211.1693, found 211.1689; $[\alpha]^{25}_D$ +25.9 (c 0.85, $CHCl_3$).

1-((3a*R*,4*S*,7a*R*)-Octahydro-3a,4-dimethyl-1*H*-inden-2-yl)-ethanone, 3. To a stirred solution of the ester (+)-**24** (0.166 g) in MeOH (1.6 mL) was added dropwise a 10% aqueous solution of KOH (1.6 mL). The mixture was stirred for 5 h at rt and the reaction was quenched with a 10% aqueous solution of HCl (until pH < 3). H_2O (20 mL) was added. The organic layer was extracted with EtOAc (3 × 25 mL), washed with brine (20 mL), and dried over anhyd $MgSO_4$. The solvent was removed under reduced pressure. The carboxylic acid was obtained as a colorless oil (0.155 g) and was used in the next step without purification. (2*S*,3a*R*,4*S*,7a*R*)-octahydro-3a,4-dimethyl-1*H*-indene-2-carboxylic acid: IR (film) 2957, 2920, 2855, 1696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (3H, d, J = 6.9 Hz), 0.89 (3H, s), 1.03−1.28 (2H, m), 1.37−1.60 (7H, m), 1.67−1.76 (1H, m), 1.81−1.90 (1H, m), 2.05−2.19 (2H, m), 2.90 (1H, dddd, J = 5.2, 8.9, 9.5, and 11.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 19.9, 21.1, 24.2, 30.7, 32.6, 33.7, 40.6, 41.5, 43.1, 47.3, 182.7; LRMS m/z (%) 196 ($M^{+\bullet}$, 14%), 178 (29), 151 (30), 109 (37), 95 (64), 81 (100); HRMS m/z $C_{12}H_{20}O_2$ $(M + Na)^+$ calcd 219.1356, found 219.1358; $[\alpha]^{25}_D$ +18.7 (c 0.42, $CHCl_3$).

To a stirred solution of the carboxylic acid (0.155 g) in anhyd Et_2O (4 mL) was added dropwise MeLi (0.60 mL, 3 M in diethoxymethane, 1.8 mmol) at 0 °C under inert atmosphere. The mixture was refluxed for 2.5 h and cooled to 0 °C. H_2O (6 mL) was added. After stirring for 10 min, the organic layer was extracted with Et_2O (3 × 25 mL) and dried over anhyd $MgSO_4$. The solvent was concentrated by reduced pressure. The crude product was purified by flash chromatography (hexanes: Et_2O, 9:1 as eluent), giving **3** (86%, 0.140 g, 0.722 mmol) as a 7:1 mixture of diastereomers, as a colorless oil. R_f 0.50 (10% Et_2O/hexanes); IR (film) 2958, 2925, 2873, 1711, 1462, 1358, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 0.77 (3H, d, J = 6.6 Hz), 0.89 (3H, s), 1.00−1.14 (1H, m), 1.24−1.58 (7H, m), 1.69−1.81 (2H, m), 1.97−2.11 (2H, m), 2.15 (3H, s), 2.89−3.06 (1H, m), (minor diastereomer) 0.80 (3H, d, J = 6.6 Hz), 2.14 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 16.4, 19.9, 21.1, 24.3, 28.9, 30.7, 31.5, 33.5, 39.9, 43.0, 47.3, 49.5, 211.1, (minor diastereomer) 16.7, 19.0, 20.9, 23.9, 28.7, 29.6, 30.4, 32.6, 41.4, 44.3, 45.7, 48.2, 211.1; LRMS m/z (%) (major diastereomer) 194 ($M^{+\bullet}$, 0.3%), 176 (3), 109 (8), 95 (7), 81 (10), 67 (8), 55 (9), 43 (100), (minor diastereomer) 194 ($M^{+\bullet}$, 2%), 124 (23), 109 (34), 95 (19), 81 (22), 71 (17), 67 (15), 55 (14), 43 (100); HRMS m/z $C_{13}H_{22}O$ $(M + H)^+$ calcd 195.1743, found 195.1741.

(2*R*,3a*R*,4*S*,7a*R*)-Methyl 2-Acetyloctahydro-3a,4-dimethyl-1*H*-indene-2-carboxylate, (+)-2. To a solution of ketone **3** (0.089 g, 0.46 mmol) in CH_2Cl_2 (4.5 mL) was added HMDS (292 μL, 0.222 mg, 1.38 mmol) and TMSI (131 μL, 0.184 g, 0.92 mmol) at −40 °C under inert atmosphere. The light yellow solution was stirred for 10 min at −40 °C and for 30 min at 0 °C. The reaction mixture was poured into a mixture of pentane (25 mL) and a saturated solution of $NaHCO_3$ (10 mL). The organic phase was separated and the aqueous phase was extracted with pentane (2 × 10 mL). The combined organic phase was dried over anhyd Na_2SO_4 and the solvent was concentrated by

(19) Ferraboschi, P.; Casati, S.; Grisenti, P.; Santaniello, E. *Tetrahedron* **1994**, *50*, 3251.

(20) Naya, K.; Hayashi, M.; Takagi, I.; Nakamura, S.; Kobayashi, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3673.

reduced pressure. The residue was filtered through a small column of silica gel (pentane as eluent) to furnish silyl-enol ether, after evaporation of pentane. The intermediate was dissolved in THF (4.5 mL) under inert atmosphere of N_2. MeLi (0.460 mL, 3 M in diethoxymethane, 1.38 mmol) was added dropwise at −40 °C. After being stirred for 10 min at −40 °C and for 10 min at 0 °C, methylcyanoformate (120 μL, 128 mg, 1.51 mmol) was added dropwise. The reaction mixture was stirred for 15 min at −40 °C and for 45 min at 0 °C. The reaction was quenched with H_2O (10 mL) and extracted with Et_2O (25 + 2 × 13 mL). The combined organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (6 mL) then brine (6 mL), and dried over anhyd Na_2SO_4. After solvent evaporation, the crude product was purified by flash chromatography (hexanes:Et_2O, 9:1 as eluent) to afford (+)-**2** (64%, 0.074 g, 0.29 mmol) as a colorless oil. R_f 0.55 (10% Et_2O/hexanes); IR (film) 2958, 2927, 1745, 1715, 1251, 1235, 1152 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.77 (3 H, d, J = 6.5 Hz), 0.91 (3H, s), 1.02−1.10 (1H, m), 1.15−1.21 (1H, m), 1.32−1.37 (1H, m), 1.42−1.46 (2H, m), 1.53−1.56 (2H, m), 1.75 (1H, d, J = 14.0 Hz), 1.87−1.93 (1H, m), 2.11−2.16 (1H, m), 2.13 (3H, s), 2.30 (1H, t, J = 13.3 Hz), 2.52 (1H, d, J = 14.0 Hz), 3.72 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3, 19.4, 20.9, 23.5, 26.5, 30.5, 32.9, 35.3, 43.5, 44.0, 46.2, 52.6, 64.4, 174.6, 203.7; LRMS m/z (%) 252 ($M^{+\bullet}$, 0.55%), 210 (75), 192 (9), 129 (26), 109 (35), 100 (20), 43 (100); HRMS m/z $C_{15}H_{24}O_3$ $(M + Na)^+$ calcd 275.1618, found 275.1628; $[\alpha]^{25}_D$ +60.8 (c 1.0, $CHCl_3$).

(2′*R*,3a′*R*,4′*S*,7a′*R*)-3a′,4′-Dimethyloctahydro-2*H*-spiro[furan-3,2′-indene]-2,4(5*H*)-dione, (+)**-28.** A solution of (+)-**2** (0.052 g, 0.21 mmol) in anhyd methanol (1.6 mL) was added dropwise with stirring to a cooled solution (0 °C) of KOH (0.070 g, 1.25 mmol) in anhyd MeOH (1 mL). After stirring for 15 min, DIB (0.133 g, 0.413 mmol) was added in small portions. The reaction mixture was stirred at 0 °C for 45 min and then a 5% aqueous solution of H_2SO_4 (1.3 mL) was added. The mixture was stirred for 35 min at 0 °C, then H_2O (3 mL) was added. The mixture was extracted with CH_2Cl_2 (20 + 2 × 6 mL). The combined organic layer was washed with brine (5 mL) and dried over anhyd $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes:Et_2O, 9:1 as eluent), affording **27** (0.036 g) as a colorless oil. **27** was dissolved in CH_2Cl_2 (1.2 mL) and acidified with TFA (12 μL). The reaction mixture was stirred overnight at rt. The resulting solution was diluted with CH_2Cl_2 (10 mL), washed with a saturated solution of $NaHCO_3$ (3 mL), and dried over anhyd $MgSO_4$. The solvent was removed under reduced pressure, giving (+)-**28** (61%, 0.030 g, 0.13 mmol) as a white solid, which was used in the next step without purification. Mp 96.0−97.1 °C; IR (KBr) 2959, 2920, 2853, 1794, 1750, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (3 H, d, J = 6.7 Hz), 0.99 (3H, s), 1.06−1.20 (1H, m), 1.46−1.59 (6H, m), 1.73−1.85 (2H, m), 1.90−2.01 (1H, m), 2.11 (1H, d, J = 13.6 Hz), 2.27−2.30 (1H, m), 4.62 (1H, d, J = 20.2 Hz), 4.69 (1H, d, J = 20.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 19.0, 20.7, 23.3, 30.6, 32.3, 39.6, 45.2, 46.8, 47.0, 51.5, 72.4, 179.2, 210.6; LRMS m/z (%) 236 ($M^{+\bullet}$, 1.0%), 124 (18), 123 (100), 109 (30), 81 (19), 41 (35); $[\alpha]^{25}_D$ +43.1 (c 1.0, $CHCl_3$).

(+)**-Bakkenolide A,** (+)**-1.** To a stirred solution of Ph_3PCH_3Br (0.130 g, 0.36 mmol) in anhyd THF (3 mL) under a strong flow of N_2 was added dropwise NaHMDS (330 μL, 1 M in hexanes, 0.33 mmol) at 0 °C. The mixture was stirred for 45 min at 0 °C resulting in a yellow solution. A solution of (+)-**28** (0.026 g, 0.11 mmol) in anhyd THF (0.5 mL) was added dropwise. The resulting light yellow solution was stirred for 1 h at rt. The reaction was quenched with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The organic phase was washed with brine (5 mL) and dried over anhyd $MgSO_4$. After solvent evaporation, the crude product was purified by flash chromatography (hexanes: AcOEt, 9:1 as eluent), affording (+)-bakkenolide A (+)-**1** (62%, 0.016 g, 0.068 mmol) as a white solid. Mp 80.3−80.6 °C (lit.[20] mp 80.5−80.6 °C); IR (KBr) 2959, 2923, 2853, 1777, 1655, 1021 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (3 H, d, J = 6.8 Hz), 0.99 (3H, s), 1.12−1.21 (1H, m), 1.41−1.64 (6H, m), 1.94−1.99 (3H, m), 2.09 (1H, t, J = 13.1 Hz), 2.24−2.30 (1H, m), 4.77 (2H, tq, J = 12.8 and 2.1 Hz), 5.11 (1H, dt, J = 2.3 and 0.7 Hz), 5.03 (1H, dt, J = 2.0 and 0.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3, 19.2, 21.0, 23.3, 30.9, 33.9, 42.3, 44.0, 46.2, 48.5, 49.8, 70.4, 105.8, 150.4, 182.6; LRMS m/z (%) 234 ($M^{+\bullet}$, 1.8%), 124 (58), 122 (34), 109 (87), 111 (52), 95 (20), 41 (100); HRMS m/z $C_{15}H_{22}O_2$ $(M + Na)^+$ calcd 257.1512, found 257.1509; $[\alpha]^{25}_D$ +16.9 (c 0.95, MeOH) {lit.[20] $[\alpha]^{20}_D$ +17 (c 1.0, MeOH)}.

Acknowledgment. The authors wish to thank FAPESP, CNPq, and CAPES for financial support.

Supporting Information Available: Spectroscopic data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.