DOI: 10.1002/ejoc.200900456

Short and Stereoselective Total Synthesis of Δ-11,13-Didehydroguaianes and -guaianolides: Synthesis of (±)-Achalensolide and (±)-Pechueloic Acid; Revision of the Structure of (+)-Rupestonic Acid

Thomas Sainte-Luce Banchelin,[a] Sébastien Carret,[a] Audrey Giannini,[a] and Jean-Pierre Deprés*[a]

Dedicated to Dr. Andrew Greene on the occasion of his 65th birthday

Keywords: Guaianes / Guaianolides / Conjugate addition / Isomerization / Total synthesis / Diastereoselectivity

(±)-Pechueloic acid (**1**), (±)-rupestonic acid (**3**), and (±)-achalensolide (**5**) (guaian-8–12-olide class) were prepared stereoselectively in only nine steps from the commercially available tropylium cation via central intermediate **6**, which is used as a general and efficient precursor to bicyclo[5.3.0]-decane sesquiterpenes. The method does not require function protection. It is highly regio- and stereoselective thanks to an efficient C-1 epimerization, a selective C-8,9 hydrogenation, and a stereocontrolled 1,6 conjugate addition of an acrylate equivalent. These Δ-11,13-didehydroguaianes and -guaianolides are good Michael acceptors and hence biologically active.

Introduction

Guaianes and guaianolides constitute one of the largest groups of natural sesquiterpenes[1] with a wide spectrum of biological activities.[1a,2,3] Guaianes such as pechueloic acid (**1**) and rupestonic acid (**3**) [and their methyl esters **2** and **4**, respectively], as well as guaianolides, like achalensolide (**5**) and xerantholide, are Δ-11,13-didehydro derivatives. This makes them good Michael acceptors and hence biologically active[3] (Figure 1). As these natural compounds are not readily available, their total synthesis is an important objective.[1,2,4] Moreover, their hydroazulene framework and their stereoselective polyfunctionalization represent further challenges. Up to now, only a limited number of short and stereoselective syntheses of these systems have been reported.[5]

(+)-Methyl pechueloate (**2**) was first isolated in 1982 from *Pechuel-Loeschea leibnitziane*[6a] together with xerantholide. Later, **2** was found in *Decachaeta scabrella*[6b] together with the parent acid **1** (pechueloic acid), achalensolide (**5**), and 11α,13-dihydroachalensolide. A first total synthesis of (+)-pechueloic acid (**1**) has been reported by Pedro and co-workers:[7] **1** was derived from (+)-dihydrocarvone in 13 steps through a sequence of reactions involving a Barton's photochemical rearrangement.[8] Rupestonic acid (**3**) was isolated in 1988 from *Artemisia rupestris* L. and converted into its methyl ester **4**.[9a] Earlier, (+)-achalansolide (**5**) had been isolated by Bohlmann and co-workers[10a] from the aerial parts of *Decachaeta thieleana* and by Hertz and co-workers[10b] from *Stevia achalansis*. Methylenelactone **5** is a potent inhibitor of aromatase found in human placental

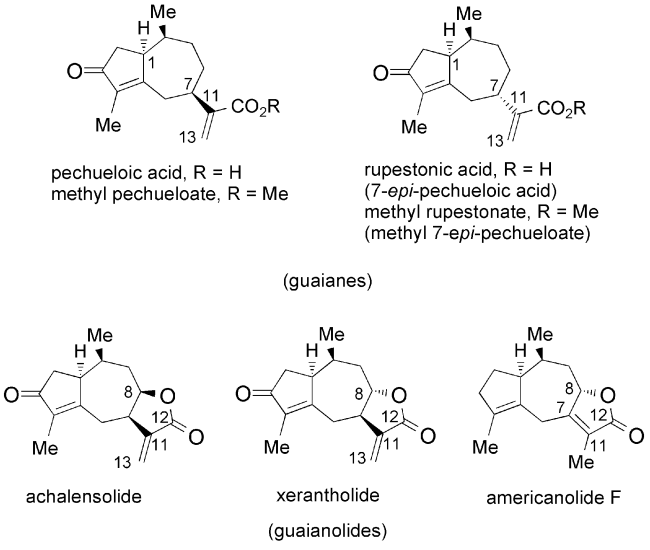


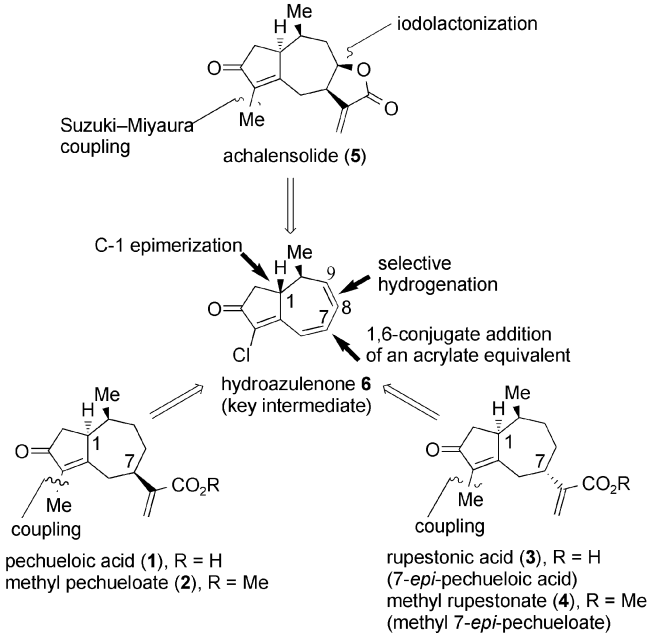
Figure 1. Δ-11,13-Didehydroguaiane and -guaianolide families.

[a] Département de Chimie Moléculaire (SERCO) UMR-5250, ICMG FR-2607, CNRS,
Bât. C, 301 rue de la Chimie, BP-53, 38041 Grenoble Cedex 9, France
Fax: +33-4-76514982
E-mail: Jean-Pierre.Depres@ujf-grenoble.fr
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900456.

microsome.[11] A first synthesis of (±)-**5** has been reported recently by Mukai and co-workers[11] and requires 27–29 steps (overall yield 0.3–0.4%) starting from D-(–)-isoascorbic acid. A key step of this synthesis is the construction of the bicyclo[5.3.0]decane skeleton by applying Pauson–Khand cyclization.

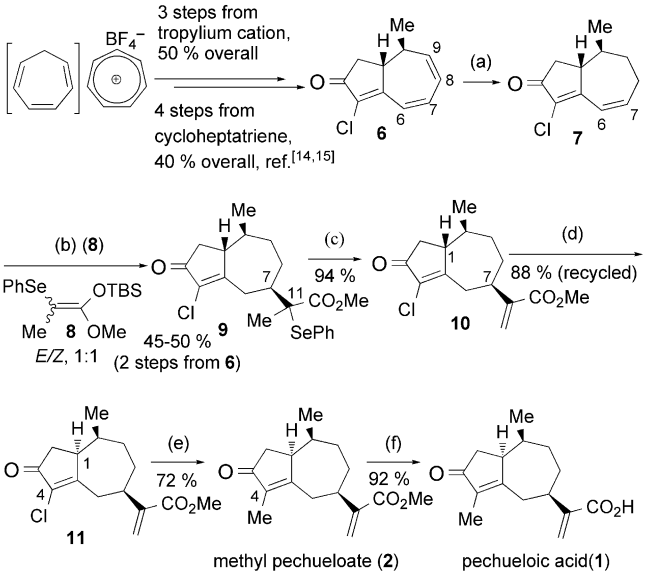
Results and Discussion

Starting from the inexpensive cycloheptatriene, we report here short syntheses, no more than ten steps long, of *rac*-**1** and its methyl ester **2** as well as the first total syntheses of *rac*-**3** and its methyl ester *rac*-**4**, and that of *rac*-achalensolide (**5**). Our retrosynthetic analysis (Scheme 1) suggested that all five compounds **1**–**5** should be derived from the same hydroazulenone **6** obtained in four steps (40% overall yield) from cycloheptatriene.[12,13] Our approach was inspired by the total synthesis of (±)-geigerin (eight steps from the tropylium cation[5b,14]) that we reported recently, which starts from our key intermediate **6**.[15] Stereodivergency at C-1 and C-7 should be available through C-1 epimerization of **6** or of a subsequent product of reaction.



Scheme 1. Retrosynthetic analysis of Δ-11,13-didehydroguaiane and -guaianolide from hydroazulenone **6**.

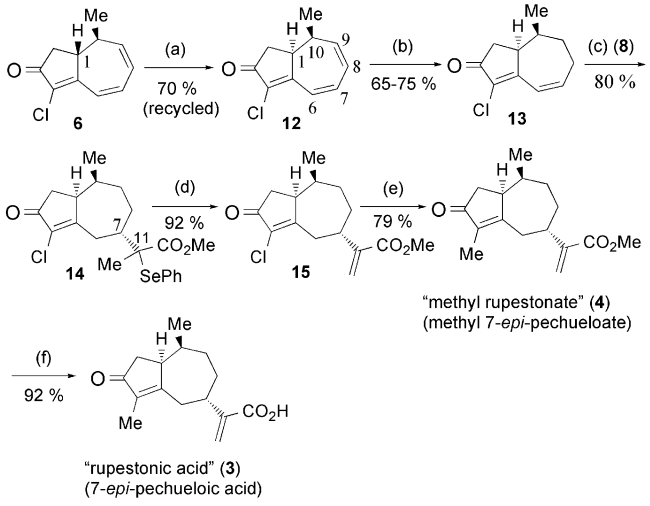
Chemoselective hydrogenation of the C-8,9 alkene moiety of **6** to afford **7** was possible by applying a Lindlar type catalyst[16] (Scheme 2). Thus, in the presence of Pd/Al_2O_3[17,18] 3:1 to 4:1 mixtures of **7** and dihydrogenated (C-6,7 and C-8,9 double bond) products were obtained. The subsequent introduction of the acrylic moiety at C-7 was realized by reaction of *tert*-butyldimethylsilyl bromoketene acetal with chlorotrienone **6**. This gave the desired 1,6 adduct in 82% yield. Unfortunately, the various elimination conditions applied to this adduct led only to the corresponding Δ-7,11-didehydro derivative (Saytzeff product). We thus investigated addition of the corresponding selenoketene acetal **8**[19] (1:1 *E*/*Z* mixture) to **6**. In the presence of $TiCl_4$ at –78 °C, the desired 1,6 adduct **9** (isomer β) was obtained with high regio- and stereoselectivity (*dr* at C-7, 95:5) in 45–50% overall yield (two steps from **6**). Oxidative elimination of the selenium moiety with hydrogen peroxide provided methyl acrylate **10** in 94% yield (ca. 44% overall yield or ca. 34% with the transformation of **7** to **10** in one pot, from **6**).



Scheme 2. Synthesis of (±)-pechueloic acid (**1**) and its methyl ester **2**. Reagents and conditions: (a) 5% Pd/Al_2O_3 (cat), H_2 (1.0–1.5 equiv.), EtOAc; (b) **8**, $TiCl_4$ (1.1 equiv.), CH_2Cl_2, –78 °C, overnight, 45–50% (over 2 steps); (c) H_2O_2 (3 equiv.), Et_3N, (2 equiv.) THF, 94%; (d) $RhCl_3(H_2O)_n$, toluene/methanol (4:1), 100 °C, 20 h, 88% (recycled twice); (e) $MeB(OH)_2$ (3 equiv.), $Pd(OAc)_2$ (0.2 equiv.), dpdb (0.4 equiv.), K_3PO_4 (2 equiv.), toluene, 60 °C, 24 h, 72%; (f) $LiOH(H_2O)_n$, THF/H_2O (95:5), 10 d, 92%; dpdb = dicyclohexylphosphanyl-2′,6′-dimethoxybiphenyl.

Epimerization at the C-1 position could be achieved on heating **10** in a 4:1 mixture of toluene/methanol to 100 °C and in the presence of $RhCl_3(H_2O)_n$ catalyst.[20] This gave a 2:5 thermodynamic mixture of **10** and **11**. Interestingly, when using classical epimerization (100 °C in 1:1 toluene/ethanol), migration of the acrylic C-11,13 double bond to the C-7,11 position was observed.[21] Flash column chromatography on silica gel separated **10** and **11** (isolated in 65%) readily. On recycling **10**, the yield of **11** climbed to 88%. Suzuki–Miyaura methylation at C-4 of chlorocyclopentenone **11** gave (±)-methyl pechueloate (**2**)[6] in 72% yield.[22] Finally, saponification of **2** with LiOH in aqueous THF afforded (±)-pechueloic acid (**1**) in 92% yield (racemic **1** is amorphous) in nine steps and with 7.6–8.5% overall yield from cycloheptatriene (nine steps, 12.3–13.7% overall yield from the commercially available tropylium cation with the transformation of **7** to **10** in two steps). Its ^1H and ^{13}C NMR spectroscopic data as well as those of its methyl ester were identical to those previously reported for the natural products.[6,7]

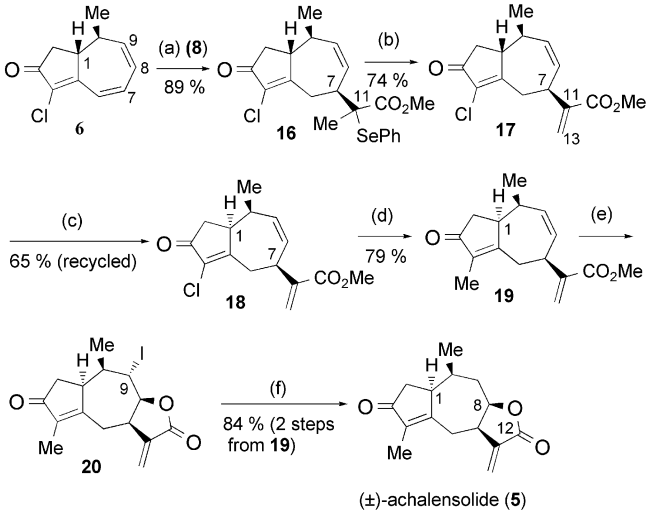
Molecular models suggested that the 1,6-conjugate addition stereoselectivity found with reaction **7** + **8** = **9** could be inverted for steric reasons through C-1 epimerization of dienone **7**. We thus studied the C-1 epimerization of **6** and established a ratio toluene/alcohol and solvent effect.[21] On heating **6** in a 1:1 mixture of toluene/ethanol to 100 °C and in the presence of $RhCl_3(H_2O)_n$ catalyst[20] afforded a 3:2 mixture of **12** and **6** with only traces of C-8,9 double bond migration.[21] After flash column chromatography **12** was isolated in 48% yield (70% considering recycling of **6**) (Scheme 3).



Scheme 3. Synthesis of "(±)-rupestonic acid" (**3**) and "(±)-methyl rupestonate" (**4**). Reagents and conditions: (a) $RhCl_3(H_2O)_n$, toluene/ethanol (1:1), 100 °C, 20 h, 70% (twice recycled); (b) 5% Pd/Al_2O_3 (cat), H_2 (1.0–1.5 equiv.), EtOAc, 65–75%; (c) **8**, $TiCl_4$ (1.0 equiv.), CH_2Cl_2, –78 °C, overnight, 80%; (d) H_2O_2 (3 equiv.), Et_3N (2 equiv.), THF, 92% (55% one pot from **13**); (e) $MeB(OH)_2$ (3 equiv.), $Pd(OAc)_2$ (0.2 equiv.), dpdb (0.4 equiv.), K_3PO_4 (2 equiv.), toluene, 60 °C, 24 h, 79%; (f) $LiOH(H_2O)_n$, THF/H_2O (95:5), 10 d, 92%; dpdb = dicyclohexylphosphanyl-2′,6′-dimethoxybiphenyl.

Controlled hydrogenation[17,18] of chlorotrienone **12** over Pd/Al_2O_3 catalyst afforded **13** in 65–75% yield as the major component of a 4:1 mixture of mono- and dihydrogenated (C-6,7 and C-8,9 double bond) products. In this case, the hydrogenation is slightly more regioselective (4:1) than in the case of **6** + H_2 = **7** (3:1 to 4:1). Conjugate addition of the selenoketene acetal[9] **8** to **13** afforded the desired 1,6 adduct **14** in 80% yield with a high regio- and stereoselectivity (*dr* at C7, 95:5). Standard oxidation of **14** with hydrogen peroxide gave the expected acrylic intermediate **15** in 92% yield (conversion of **13** to **15** can be realized in a one-pot operation in 55% yield). Suzuki–Miyaura methylation of the chloroenone **15**[22] afforded (±)-methyl rupestonate (**4**) (methyl-7-*epi*-pechueloate) in 79% yield (m.p. 55–57 °C). Finally, saponification of **4** afforded *rac*-rupestonic acid (**3**) (7-*epi*-pechueloic acid; m.p. 140 °C[23]) in 92% yield (Scheme 3, in nine steps from cycloheptatriene with 7.4–8.4% overall yield or in nine steps with 12.3–14.0% overall yield, from the tropylium cation, with the transformation of **13** to **15** in two steps). The structure of **3** was confirmed by single-crystal X-ray diffraction studies.[24] Surprisingly, the ^1H and ^{13}C NMR spectroscopic data of *rac*-**3** and its methyl ester *rac*-**4** were different from those reported in the literature for the (+)-rupestonic acid isolated from *Artemisia rupestris* L.[9a]

In order to build the α-methylene-γ-butyrolactone of *rac*-achalansolide (**5**) by iodolactonization, it was necessary to maintain the C-8,9 double bond (Scheme 4). Consequently, 1,6-conjugate addition of selenoketene acetal[16] **8** to hydroazulenone **6** was attempted. To our delight, it afforded a 1:1 mixture of the expected 1,6 adducts **16** (mixture of C-11 epimers) with high regio- and good stereoselectivity (*dr* at C-7: > 4:1). The purified mixture of four isomers (isolated in 89% yield) was treated with hydrogen peroxide to give acrylate **17**, which was easily isolated by flash chromatography in 74% yield. Its C-1-epimerization with $RhCl_3$ catalyst in toluene/methanol (4:1) at 100 °C gave a 5:3 thermodynamic mixture of **17** and **18**, whereas in 1:1 toluene/ethanol (100 °C), migration of the double bond from C-8,9 to C-6,7 was observed.[21] Compound **17** was easily removed by flash chromatography and **18** was isolated in 35% yield (65% after recycling **17** twice). Suzuki–Miyaura methylation of chloroenone **18**[22] afforded **19** in 79% yield. Saponification of **19** furnished the corresponding lithium carboxylate, which was immediately subjected to the iodolactonization conditions.[25] This afforded **20**, which was reduced under radical conditions with nBu_3SnH to give *rac*-**5** in 84% yield (ten steps from cycloheptatriene with 11.4% overall yield or nine steps from the commercially available tropylium cation with 14.2% overall yield) (Scheme 4).



Scheme 4. Synthesis of (±)-achalensolide (**5**). Reagents and conditions: (a) **8**, $TiCl_4$ (1.1 equiv.), CH_2Cl_2, –78 °C, overnight, 89%; (b) H_2O_2 (3 equiv.), Et_3N (2 equiv.), THF, 74%; (c) $RhCl_3(H_2O)_n$, toluene/methanol (4:1), 100 °C, 20 h, 65% (twice recycled); (d) $MeB(OH)_2$ (3 equiv.), $Pd(OAc)_2$ (0.2 equiv.), dpdb (0.4 equiv.), K_3PO_4 (2 equiv.), toluene, 60 °C, 24 h, 79%; (e) $LiOH(H_2O)_n$, THF, CO_2, KI, CH_3CN; (f) nBu_3SnH (1.5 equiv.), Et_3B (0.1 equiv.), O_2, toluene/THF (85:15), 84% (over 2 steps); dpdb = dicyclohexylphosphanyl-2′,6′-dimethoxybiphenyl.

Conclusions

In conclusion, we have developed a highly efficient total synthesis of (±)-pechueloic acid (**1**) and of its methyl ester **2**. We also disclose the first total synthesis of (±)-7-*epi*-pechueloic acid ("rupestonic acid") (**3**) and of its methyl ester **4**, as well as a short total synthesis of (±)-achalensolide (**5**) starting from the inexpensive cycloheptatriene. The method does not require function protection and deprotection steps. It is highly regio- and stereoselective thanks to the very effective 1,6-conjugate addition of a selenoketene acetal (acrylate equivalent), the face selectivity of the reaction being controlled by the configuration of the bridgehead center C-1 of the azulenone moiety. Complementary studies are undergoing in our group to generalize this strategy to other members of this family of natural compounds, and especially to guaianes with a *trans*-annulated lactone such as xerantholide,[6b] and to Δ-7,11-didehydroguaianes such as americanolide F[26] (Figure 1).

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for **1**–**5**, **10**–**13**, **15**, **17**, **18** and **19**, ^{1}H and ^{13}C NMR spectra for **1**–**5**, **10**, **11**, **15**, **17**, **18** and **19**, ORTEP drawing of **3**.

Acknowledgments

This work was supported by the French Ministry of Research for a fellowship award to T. S-L. B and by the University Joseph Fourier and the CNRS (UMR-5250, ICMG FR-2607). We thank Prof. Pierre Vogel for his assistance for this manuscript and for his interest in this research, Dr. Andrew Greene for his interest in our work, and Drs. André Durif and Christian Philouze for the X-ray structure determination.

[1] a) M. B. Fraga, *Nat. Prod. Rep.* **2002**, *19*, 650–672; M. B. Fraga, *Nat. Prod. Rep.* **2003**, *20*, 392–413; M. B. Fraga, *Nat. Prod. Rep.* **2004**, *21*, 669–693; M. B. Fraga, *Nat. Prod. Rep.* **2005**, *22*, 465–486; M. B. Fraga, *Nat. Prod. Rep.* **2006**, *23*, 943–972; M. B. Fraga, *Nat. Prod. Rep.* **2007**, *24*, 1350–1381; b) J. D. Connolly, R. A.Hill, *Mono- and Sesquiterenoids*, *Dictionary of Terpenoids*, Chapman & Hall, London, **1991**, vol. 1, pp. 476–523; c) S. P. Andrews, M. Ball, F. Wierschem, E. Cleator, S. Olivier, K. Högenauer, O. Simic, A. Antonello, U. Hünger, M. D. Smith, S. V. Ley, *Chem. Eur. J.* **2007**, *13*, 5688–5712.

[2] M. Ball, S. P. Andrews, F. Wierschem, E. Cleator, M. D. Smith, S. V. Ley, *Org. Lett.* **2007**, *9*, 663–666.

[3] a) S. M. Kupchan, M. A. Eakin, A. M. Thomas, *J. Med. Chem.* **1971**, *14*, 1147–1152; b) S. M. Kupchman, T. J. Giacobbe, I. S. Krul, A. M. Thomas, M. A. Eakin, D. C. Fessler, *J. Org. Chem.* **1970**, *35*, 3539–3543.

[4] a) C. H. Heathcock, *The Total Synthesis of Natural Products* (Ed.: J. Apson), Wiley Interscience, New York, N. Y., **1973**, vol. 2, pp. 197–558; b) M. C. Pirrung, *The Total Synthesis of Natural Products*, (Ed.: D. Goldmsith), Wiley Interscience, New York, N. Y., **2000**, vol. 11; c) G. Blay, L. Gardona, B. Garcia, J. R. Pedro, *Studies in Natural Products Chemistry* (Ed.: Attaur-Rahman), Elsevier Science, Amsterdam, **2000**, vol. 24, pp. 53–59; d) T. L. Ho, *Carbocycle Construction in Terpene Chemistry*, VCH, New York, N. Y., 1**988**; e) S. Carret, Y. Coquerel, A. Giannini, T. Sainte-Luce Banchelin, J.-P. Deprés, *Actual. Chim.* **2006**, *294*, 23–27.

[5] a) E. Lee, J. W. Yoon, Y. Sun, Y. K. Kim, M. Yun, S. Kim, *J. Am. Chem. Soc.* **1997**, *119*, 8391–8392; b) S. Carret, J.-P. Deprés, *Angew. Chem. Int. Ed.* **2007**, *46*, 6870–6873.

[6] a) F. Bohlmann, N. Borthakur, *Phytochemistry* **1982**, *21*, 1160–1162; b) M. Miski, D. H. de Luengo, T. J. Mabry, *Phytochemistry* **1987**, *26*, 199–200.

[7] G. Blay, B. Garcia, E. Molina, J. R. Pedro, *Tetrahedron* **2007**, *63*, 9621–9626.

[8] D. H. R. Barton, J. E. D. Levisalles, *J. Chem. Soc.* **1958**, 4518–4523.

[9] a) G. S. Xu, X. Y. Chen, D. Q. Yu, *Acta Pharm. Sin.* **1988**, *23*, 122–125; b) Y. Ma, H. A. Aisha, S. Aibai, T. Zhang, Y. Ito, *J. Chromatogr. A* **2005**, *1076*, 198–201; c) H. A. Aisa, J.-P. Yong, O.-Y. Lv, T. Wu, *Acta Crystallogr., Sect. E* **2008**, *64*, 479.

[10] a) V. Castro, F. Ciccio, S. Alvarado, F. Bolmann, G. Schmeda-Hirschmann, J. Jakupovic, *Liebigs Ann. Chem.* **1983**, 974–981; b) J. C. Oberti, V. E. Sosa, W. Hertz, J. S. Prasad, V. L. Goedken, *J. Org. Chem.* **1983**, *48*, 4038–4043.

[11] T. Hirose, N. Miyakoshi, C. Mukai, *J. Org. Chem.* **2008**, *73*, 1061–1066.

[12] For an example of a versatile key intermediate, see the efficient stereocontrolled total synthesis of bakkenolides functionalized on the A and B ring: a) O. Hamelin, Y. Wang, J.-P. Deprés, A. E. Greene, *Angew. Chem. Int. Ed.* **2000**, *39*, 4314–4316; b) O. Hamelin, J.-P. Deprés, A. E. Greene, B. Tinant, J.-P. Declercq, *J. Am. Chem. Soc.* **1996**, *118*, 9992–9993.

[13] Step economy and atom economy: a) K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem. Int. Ed.* **2000**, *39*, 44–122; b) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695–705; c) P. A. Wender, J. L. Bariza, S. E. Brener, M. O. Clarke, G. G. Gamber, J. C. Horan, T. C. Jessop, C. Kan, K. Pattabiraman, T. J. Williams, *Pure Appl. Chem.* **2003**, *75*, 143–145; d) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Chemistry*, Wiley-VCH, Weinheim, **2006**; e) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40–49.

[14] The overall yield from the tropylium cation has been improved from 43–45% to 50% overall yield (see ref.[15]) by elimination of HCl in THF/DMF (7:3) in the presence of two equivalents of pyridine to generate hydroazulenone **6** in soft conditions.

[15] a) S. Carret, J.-P. Deprés, *Tetrahedron Lett.* **2008**, *49*, 5642–5644; b) Y. Coquerel, A. E. Greene, J.-P. Deprés, *Org. Lett.* **2003**, *5*, 4453–4455; c) J.-P. Deprés, A. E. Greene, *J. Org. Chem.* **1980**, *45*, 2036–2037.

[16] Inversion of the order of 1,6-conjugate addition of **8** and hydrogenation reaction did not afford the desired product **7**. Actually, the C-11,13 double bond of acrylate **17** is more reactive than the C-8,9 one in the presence of a Lindlar type catalyst.

[17] A volume of 1–1.5 equiv. of hydrogen has been used by progressive addition with a syringe. See ref.[21].

[18] a) C. R. Lederhos, P. C. L′argentiere, N. S. Figoli, *Ind. Eng. Chem. Res.* **2005**, *44*, 1752–1756; b) G. Liu, Z. Mi, L. Wang, X. Xang, *Ind. Eng. Chem. Res.* **2005**, *44*, 3846–3851.

[19] The *tert*-butyldimethylsilyl selenoketene acetal (1:1 *E*/*Z* mixture) **8** has been quantitatively obtained from the corresponding α-selenoester (see: L. Lebarillier, F. Outurquin, C. Paulnier, *Tetrahedron* **2000**, *56*, 7483–7493 and references cited therein) by using lithium diisopropylamide (LDA) as base at –78 °C and by inverse addition.

[20] a) R. Cramer, *J. Am. Chem. Soc.* **1967**, *89*, 1633–1639; b) J. Andrieux, D. H. R. Barton, H. Patin, *J. Chem. Soc. Perkin Trans. 1* **1977**, 359–363.

[21] Studies of chemoselective hydrogenation of the C-8,9 alkene moiety and solvent effects in C-1 epimerization are described in our previous article (see: M. Calancea, S. Carret, J.-P. Deprés, *Eur. J. Org. Chem.* **2009**, 3134–3137).

[22] S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2004**, *43*, 1871–1876.

[23] A melting point of 132–133 °C is mentioned for (+)-rupestonic acid, but surprisingly the ^{1}H and ^{13}C NMR spectroscopic data resemble those of pechueloic acid. See ref.[9a]

[24] Crystallographic data for (±)-**3** ($C_{15}H_{20}O_3$): monoclinic space group $P2_1/c$, a = 8.651(2) Å, b = 16.431(2) Å, c = 9.74(1) Å, β

= 93.62(4)°, V = 1381(1) Å^3, $\rho_{calcd.}$ = 1.194 g cm^{-3}, Z = 4, R_1 = 0.0571 [$I > 2.0\sigma(I)$], R_w = 0.0809 (all data), 3043 measured reflexions, 2923 independent reflections and R = 0.0571 [$I > 2.0\sigma(I)$]; diffractometer: CAD4-Enraf–Nonius. CCDC-714117 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[25] P. A. Grieco, N. Marinovic, M. Miyashita, *J. Org. Chem.* **1974**, *40*, 1670–1672.

[26] A. D. Rodriguez, A. Boulanger, *J. Nat. Prod.* **1997**, *60*, 207–211.

Received: April 27, 2009
Published Online: June 19, 2009

