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New approach to paricalcitol synthesis

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Paricalcitol, an analog of vitamin D, is used as a drug for the prevention and treatment of secondary hyperparathyroidism. In this paper, a new strategy for the synthesis of paricalcitol is described. This approach includes three main improvements: one-pot regioselective ozonization cleavage of the side-chain and methylene at C-19, free-radical reduction removal of the OH group formed at C-19, and side-chain assembly using a Wittig reaction. These are all new strategies for the synthesis of 19-nor-vitamin D_2 compounds.

paricalcitol, synthesis, ozonization, Wittig reaction

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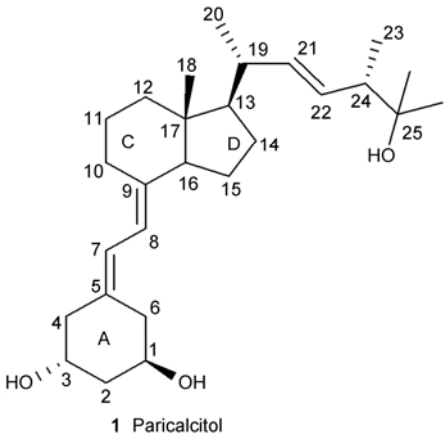
Paricalcitol (**1**, Figure 1), a second-generation vitamin D receptor (VDR) activator, has been developed as a drug for the prevention and treatment of secondary hyperparathyroidism (SHPT) and of period III and IV chronic kidney diseases (CDK) [1]. The effect of paricalcitol on intestinal calcium resorption is less than that of calcitriol; this avoids undesirable hypocalcaemia [2]. Paricalcitol also retains significant immunomodulatory activity, comparable to that of calcitriol [3]. The immunomodulatory potency of paricalcitol makes it a drug of interest in the therapy of chronic immune-mediated inflammatory diseases.

Paricalcitol is of wide interest because of its known and potential applications. The original synthesis [4,5] used a convergent strategy. Three key parts were prepared respectively from vitamin D_2, quinic acid, and methyl 2-methyl-3-hydroxypropionate, and assembled to form paricalcitol in 19 steps. Another synthesis [6] started from ergosterol and used ozonization, with Julia coupling as the key steps. A modification of the introduction of the side-chain of paricalcitol was reported by Ng and co-workers [7], who used a Wittig-Horner reaction instead of Julia olefination. The most recent synthesis [8] still started from vitamin D_2 and involved 17 steps. The assembly of side-chains and



1 Paricalcitol

Figure 1 Structure of paricalcitol.

cleavage of the methylene group on ring A of vitamin D_2 were achieved by ozonization/Julia olefination and dihydroxylation/oxidation with $NaIO_4$, respectively.

Large-scale, efficient, convenient synthesis of paricalcitol is still a challenge. We therefore tried to find an efficient synthetic method. First, we tried to improve the main conversion steps, especially removal of the C-19 methylene group and assembly of the side-chain. It was found that the side-chain and C-19 methylene can be cleaved selectively in

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one-pot ozonization instead of by ozonization/dihydroxylation/oxidation cleavage of $NaIO_4$; the formed C-19 OH group was removed by free-radical reduction instead of reduction using $LiAlH_4$, and the side-chain was assembled using a Wittig reaction instead of Julia coupling/olefination. These improvements made the synthesis more convenient and efficient.

The synthesis started from commercially available vitamin D_2, which has a skeleton similar to that of paricalcitol. Because both the methylene group and the side-chain can be cleaved by ozonization, cleavage can be performed in one pot using ozone. Reaction of vitamin D_2 with *p*-toluenesulfonyl chloride (TsCl) in pyridine gave tosylate **3** in 88% yield. Treatment of **3** with K_2CO_3 in methanol gave compound **4** in 67% yield [9], in which one double bond was protected and the methylene group on ring A and the double bond of the side-chain remained. Allylic oxidation of **4** to introduce 1-α-OH proceeded by allylic oxidation with SeO_2 [10]. It was found that *t*-butyl hydroperoxide (TBHP) is a better co-oxidant than *N*-methylmorphine *N*-oxide (NMO). In dichloromethane (CH_2Cl_2)/methanol (MeOH) (3∶1, v/v) as solvent and using SeO_2/TBHP and SeO_2/NMO as oxidants, **5** yielded in 58% and 40% yields from **4**, respectively. Importantly, both of these two oxidations gave a single 1-α-OH product **5** after column chromatography (Figure 2).

The first important step in the synthesis is the one-pot ozonization of the methylene group and the side-chain. Compound **5** was treated with either $MeOCH_2Cl$ and diisopropylethylamine (DiPEA) in CH_2Cl_2 or acetic anhydride (Ac_2O) and pyridine (Py) in CH_2Cl_2 or *t*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in *N*,*N*-dimethylformide (DMF) to protect the OH group. The corresponding protected products **6a**, **6b**, and **6c** were formed in 90%, 86%, and 80% yields, respectively. The ozonization of each of **6a**, **6b**, and **6c** was carried out in CH2Cl2/MeOH (1∶1, v/v) at –65°C. After the starting material had all reacted, $NaBH_4$ was added to quench the reaction. Compounds **7a**[1], **7b**, and **7c** were obtained from the corresponding substrates in 62%, 40%, and 52% yields, respectively, as single isomers (Figure 3). Neither the configurations of **7a–7c**, nor those of the corresponding subsequent compounds **8–13**, are known.

The second challenge in the synthesis is the removal of the OH group on C-19 of compound **7a**. First, **7a** was reacted with Ac_2O and pyridine in CH_2Cl_2 to protect the primary OH. In accordance with the literature [11], **8a** was

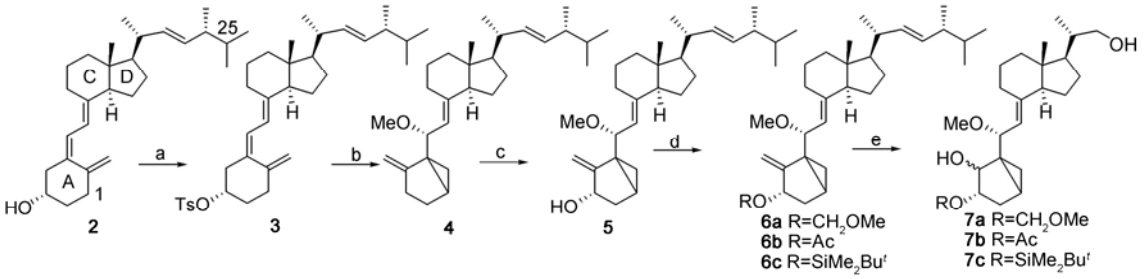

Figure 2 Synthesis of intermediates **7a–7c**. Reagents and conditions: a) TsCl, pyridine, rt, 10 h, 88%; b) K_2CO_3, MeOH, reflux, 5 h, 67%; c) SeO_2, TBHP, CH_2Cl_2, MeOH, reflux, 58%; d) $MeOCH_2Cl$, DiPEA, CH_2Cl_2, rt, 7 h, 90% yield for **6a**; Ac_2O, pyridine, CH_2Cl_2, rt, 6 h, 86% yield for **6b**; TBDMSCl, imidazole, DMF, 80% yield for **6c**; e) i. O_3, CH_2Cl_2, MeOH; ii. $NaBH_4$; –78°C, 62% for **7a**, 40% for **7b**, and 52% for **7c**.

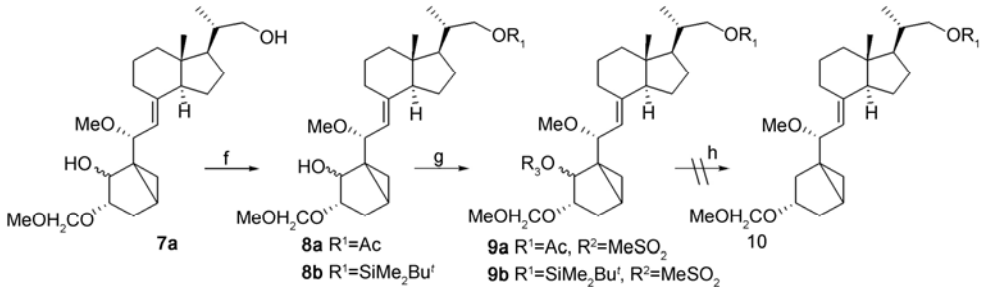

Figure 3 Removal of OH group on ring A of **8a**. Reagents and conditions: f) Ac_2O, pyridine, CH_2Cl_2, rt, 3 h, 85% for **8a**; TBDMSCl, imidazole, DMF, rt, 1 h, 78% for **8b**; g) **9a**: MsCl, Et_3N, 0°C, 1 h; **9b**: i. NaH, THF, CS_2, reflux, 3 h; ii. MeI, reflux, 3 h; 67% for **9b**; **9c**: 1,1'-diimidazole carbonyl, DMAP, CH_2Cl_2, 1 h, 84% for **9c**; **9d**: MsCl, Et_3N, CH_2Cl_2; h) $LiAlH_4$, THF, rt, for **9a** and **9d**; Bu_3SnH, AIBN, toluene, reflux, for **9b** and **9c**.

1) The spectrum data of **7a**: ^{1}H NMR (300 MHz, δ) 0.57 (3H, s), 0.65 (1H, m), 0.80–0.87 (2H, m), 1.04 (3H, d, J = 6.6 Hz), 1.27–1.35 (3H, m), 1.47–1.55 (3H, m), 1.61–1.67 (3H, m), 1.84–2.01 (6H, m), 2.81 (1H, d, J = 10.5 Hz), 3.05 (1H, s), 3.16 (3H, s), 3.34 (3H, s), 3.50 (1H, m), 3.62 (1H, dd, J = 2.1, 10.5 Hz), 3.65 (1H, dd, J = 2.4, 6.9 Hz), 3.98 (1H, d, J = 4.2 Hz), 4.58 (1H, d, J = 9.6 Hz), 4.59 (2H, m), 4.75 (1H, d, J = 9.6 Hz). ^{13}C NMR (75 MHz, δ) 9.6, 11.8, 16.8, 18.2, 22.2, 23.6, 27.1, 29.3, 31.0, 34.3, 39.0, 40.3, 45.5, 52.8, 55.5, 55.6, 67.7, 72.6, 73.9, 77.2, 96.2, 119.3, 144.0. ESI-HRMS (*m/z*) [M+Na$^+$] 431.2763 (Calc. 431.2768).

mesylated with methanesulfonyl chloride (MsCl) and triethylamine (Et_3N) in CH_2Cl_2 to form compound **9a** and the crude **9a** was subsequently reduced using $LiAlH_4$ in THF before purification. Unfortunately, these two reaction steps were messy, and **10** was not found. Detailed investigations found that very little **9a** was formed in the mesylation. To avoid the effect of the actyl group in the reduction, **8b** was prepared from **7a** in 78% yield. The mesylation of **8b**, followed by reduction of **9b**, was also messy and failed to give **10**. Investigation of the side-products proved that the three-membered ring is unstable under these reductive conditions. So, another approach was proposed, as shown in Figure 4.

Compound **8a** was treated with acetic acid (AcOH) in dimethyl sulfoxide (DMSO) and **11** was formed in 72% yield as a single isomer after purification by column chromatography [12–15]. The double-bond configuration of compound **11** is not known for certain and those of the subsequent products **12–19** are also unclear. The protection of **11** with $MeOCH_2Cl$/DiPEA gave an OH-free product in which the two OH groups of **11** were protected. So, a bulky group TBDMS was used as the protection group and **12** was obtained in 75% yield. Procedures similar to the protection of **8a** converted **12** to **13a–13c**. Compounds **13a**, **13b**, and **13c** were prepared in 38%, 57%, and 78% yields, respectively. Compound **13a** was reduced with $LiAlH_4$ in THF and only a trace of **14** was found. Free-radical reduction of **13b** with tributyltin hydride (Bu3SnH) and azodiisobutrnitrile (AIBN) in toluene under reflux [16] gave the desired dehydroxylated product **14** in 48% yield. However, the reduction of **13c** only gave **12** along with some useless products.

At this point, the skeleton of the target compound had been constructed. The last important step is to introduce a new side-chain. Julia olefination [8] and the Wittig reaction [7] are general methods for this kind of conversion. As in the scheme shown in Figure 4, **14** was deprotected with K_2CO_3 in MeOH, followed by Swern oxidation; aldehyde **16**[2] was formed in 62% yield from **14**. The side-chain **17** was prepared from ester **20**. Grignard reaction of **20** with 3.0 equivalents of MeMgBr in Et_2O gave **21** in quantitative yield. Compound **21** reacted with TsCl and pyridine in CH_2Cl_2 to form tosylate **22** in 85% yield [17]. Nucleophilic substitution of **22** with NaI in acetone gave **23** in 77% yield. After protection, **24**[3] was heated with PPh_3, without a solvent, and **17** was formed. Trituration of the reaction mixture with Et_2O and CH_2Cl_2 by turns gave the purified side-chain **17**. The yields of **17** from **23** are 30%–60%, depending on the protecting group. Sulfone **25** was prepared according to the literature method [18].

As the scheme shown in Figure 4, compound **17a** was

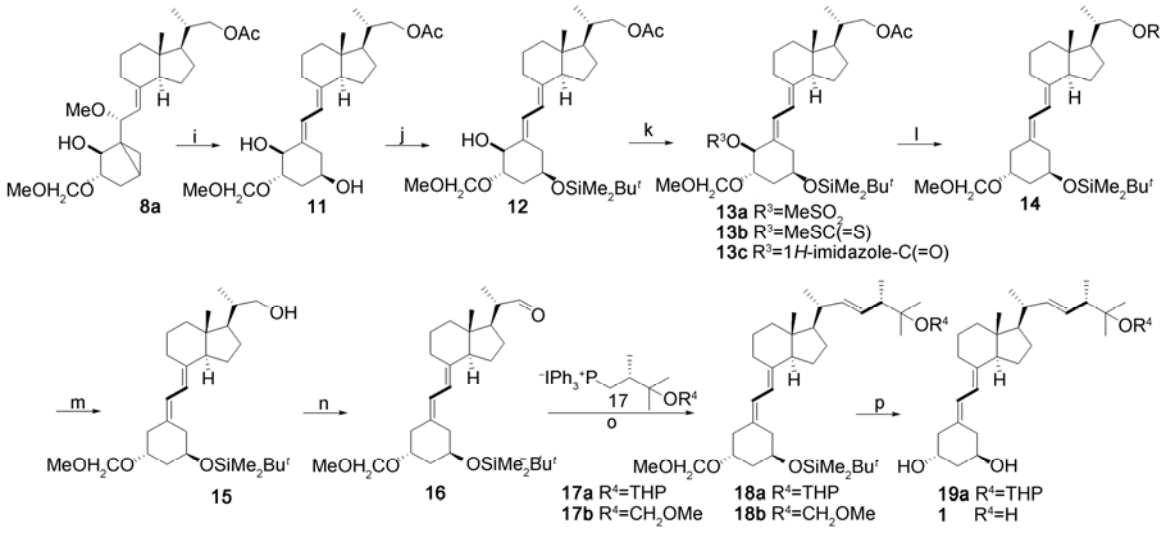

Figure 4 Alternative method for removing the OH group of **8a**. Reagents and conditions: i) AcOH, DMSO, 50°C, 1 h, 72%; j) TBDMSCl, imidazole, DMF, rt, 2 h, 75%; k) **13a**: MsCl, Et_3N, CH_2Cl_2, 0°C; **13b**: i. NaH, THF, CS_2, reflux, 3 h; ii. MeI, reflux, 3 h, 57% for **13b**; **13c**: 1,1'-diimidazole carbonyl, DMAP, CH_2Cl_2, rt, 78% for **13c**; l) $LiAlH_4$, THF, rt, for **13a**; Bu_3SnH, AIBN, toluene, reflux, 1 h, 48% for **13b**; m) K_2CO_3, MeOH, reflux, 3 h; n) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78°C, 62% for two steps; o) i. *n*-BuLi, THF, −78°C–rt, 1 h; ii. 17, THF, 10 h, 72% for **18a**, 63% for **18b**; p) **19a**: PPTs, 95% EtOH, reflux, 2 h, 70%; **1**: $ZrCl_4$, *i*-PrOH, reflux, 5 h, 65%.

2) The spectrum data of **16**: ^{1}H NMR (300 MHz, δ) 0.05 (6H, s), 0.57 (3H, s), 0.86 (9H, s), 1.12 (3H, d, J = 6.9 Hz), 1.40 (1H, m), 1.50–1.75 (8H, m), 1.87–2.02 (4H, m), 2.06–2.16 (1H, m), 2.29–2.43 (3H, m), 2.54 (1H, dd, J = 6.0, 14.1 Hz), 2.82 (1H, dd, J = 3.9, 10.5 Hz), 3.34 (3H, s), 3.95–4.03 (2H, m), 4.64 (2H, dd, J = 6.6, 9.3 Hz), 5.84 (1H, d, J = 11.1 Hz), 6.20 (1H, d, J = 11.7 Hz), 9.57 (1H, s). ^{13}C NMR (75 MHz, δ) 4.7, 12.4, 13.5, 18.1, 22.6, 23.1, 25.8, 26.4, 28.6, 33.5, 40.1, 40.7, 45.8, 46.0, 49.7, 51.3, 55.2, 55.4, 67.8, 72.7, 94.8, 116.2, 121.8, 133.5, 140.5, 205.0. ESI-HRMS (*m/z*) [M+K$^+$] 529.3118, [M+Na$^+$] 513.3370 (Calc. 513.3371), [M+NH$_4^+$] 508.3826.

3) The spectrum data of **24c**: ^{1}H NMR (300 MHz, δ) 1.08 (3H, d, J = 5.7 Hz), 1.12 (3H, s), 1.23 (3H, s), 1.97 (1H, m), 2.85 (1H, dd, J = 9.3, 11.1 Hz), 3.35 (3H, s), 3.68 (1H, dd, J = 1.8, 9.3 Hz), 4.67 (2H, m).

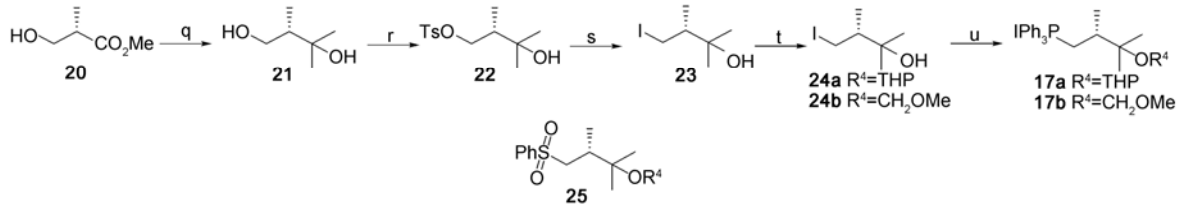

Figure 5 Side-chain preparation. Reagents and conditions: q) MeMgBr, Et_2O, reflux, 3 h, 98%; r) TsCl, pyridine, rt, 2 h, 85%; s) NaI, acetone, reflux, 10 h, 77%; t) 3, 4-DHP, cat. *p*-TsOH, CH_2Cl_2, rt, overnight, 83% for **24a**; $MeOCH_2Cl$, DiPEA, CH_2Cl_2, rt, 4 h, 88% for **24b**; u) PPh_3, 100°C, 40 h, 60% for **17a** and 66% for **17b**.

deprotonated with *n*-BuLi at –78°C, and then the generated anion reacted with **16** *in situ* to form **18a** in 72% yield in a 4∶3 *trans*/*cis* ratio. The mixture cannot be separated by flash silica-gel column chromatography and the *trans*/*cis* ratio was determined by ^{1}H NMR. Other strong bases such as MeLi, PhLi, and potassium *t*-butoxide (*t*-BuOK) did work in this reaction, but did not improve the conversion rate or the selectivity. Similar results were also observed in the reaction of **17b** with **16**. The yield of **17b** was 63%. Unexpectedly, a similar reaction of **16** and **25**, using a literature procedure [18], did not give any useful products.

Removal of the protecting groups on **18a** and **18b** is a challenge. Many methods, including protonic conditions and Lewis acid conditions, have been reported to remove $SiMe_2Bu^t$, THP, THF, and CH_2OMe. However, the THP of **18a** and THF of **18b** cannot be removed. Reactions with *p*-toluenesulfonic acid (*p*-TsOH) in aqueous ethanol, 3 mol/L HCl in methanol, $MgBr_2$ in THF, Dowex resins, $ZrCl_4$ in *i*-propanol (*i*-PrOH), pyridium *p*-toluenesulfonate (PPTs)in ethanol (EtOH), Py·HF in THF, tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF), etc. simply converted **18a** to **19a**. Strong Lewis acids such as $AlCl_3$ and $BF_3{\cdot}Et_2O$ did not remove THP and THF, and also decomposed most of the substrate. After screening a great many reagents, solvents, and reaction temperatures, **1**[4] was obtained in 65% yield by refluxing **18b** with $ZrCl_4$ in *i*-PrOH.

In conclusion, a new synthesis of paricalcitol was achieved in 14 steps. This approach had major improvements on previous syntheses. First, the C-19 methylene group was removed by ozonization and free-radical reduction; this is more efficient strategy than that trough dihydroxylation, cleavage, protection, and reduction. Second, the side-chain was assembled by ozonization and a Wittig reaction rather than by ozonization, Julia coupling, and olefination; this is a shorter conversion and is also heavy-metal-free conversion. More importantly, the ozonization of the side-chain and methylene group was a one-pot reaction; this is the first use of selective ozonization in the synthesis of paricalcitol. This synthesis is not only important for the research on and development of paricalcitol, but is also of value in research on vitamin D analogs. This is the shortest synthesis of paricalcitol to date, and will be applicable after further modifications.

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1 Martin K J, Gonzalez E A, Gellens M, et al. J Am Soc Nephrol, 1998, 9: 1427–1432
2 Deluca H F, Schnoes H K, Perlman K L, et al. European Patent Application, EP0387077, 1990
3 Truitt G A, Benjamin W R, Devens B H, et al. United States Patent, US4749710, 1985
4 Deluca H F, Schnoes H K, Perlman K L, et al. United States Patent, US5281731, 1994
5 Deluca H F, Schnoes H K, Perlman K L. United States Patent, US5086191, 1992
6 Toyoda A, Nagai H, Konuki K. International Application Published Under Property Cooperation Treaty (PCT), 2008, WO2008053961
7 Ng C S, Wei C P. United States Patent, US007491712, 2009
8 Bader T, Stutz A, Bichsel H U, et al. International Application Published Under Property Cooperation Treaty (PCT), WO2010009879
9 Okamura W H, Zhu G D, Hill D K, et al. J Org Chem, 2002, 67: 1637–1650
10 Knutson J C, Mazess R B, Bishop C W. United States Patent, US6903083, 2005
11 Deluca H F, Schnoes H K, Perlman C L, et al. United States Patent, US5587497, 1996
12 Wang Q L, Huang Q G, Chen B, et al. Angew Chem Int Ed, 2006, 45: 3651–3653
13 Barton D H R, McCombie S W. J Chem Soc Perkin Tran, 1975, 2: 1574–1585
14 Barton D H R, Lobberding D C A, Zard S Z. Tetrahedron, 1986, 42: 2329
15 Crich D, Quintero L. Chem Rev, 1989, 89: 1413–1432
16 Sheves M, Mazur Y. J Am Chem Soc, 1975, 97: 6249–6250
17 Beszant S, Giannini E, Zanoni G, et al. Eur J Org Chem, 2003, 20: 3958–3968
18 Deluca H F, Schnoes H K, Perlman K L. United States Patent, US5260290, 1993

4) The spectrum data of paricalcitol (**1**): ^{1}H NMR (300 MHz, δ) 0.58 (3H, s), 0.99 (6H, m), 1.18 (3H, s), 1.26 (3H, s), 1.38 (1H, m), 1.46 (3H, m), 1.67–1.83 (8H, m), 1.92–2.00 (3H, m), 2.19–2.27 (2H, m), 2.48 (1H, m), 2.71 (1H, m), 2,79 (1H, m), 4.05 (1H, m), 4.11 (1H, m), 5.18 (1H, dd, J = 9.9, 11.1 Hz), 5.35 (1H, dd, J = 9.6, 11.1 Hz), 5.84 (1H, d, J = 11.1 Hz), 6.30 (1H, d, J = 11.1 Hz). ^{13}C NMR (75 MHz, δ) 12.4, 16.4, 21.7, 21.3, 22.2, 25.4, 26.6, 26.9, 27.7, 28.9, 34.0, 37.0, 40.3, 42.1, 42.7, 44.6, 45.6, 56.2, 60.4, 67.1, 72.7, 115.3, 123.2, 128.2, 131.3, 138.3, 142.7. ESI-HRMS (*m/z*) [M+NH_4^+] 434.3623 (Calc. 434.3629).