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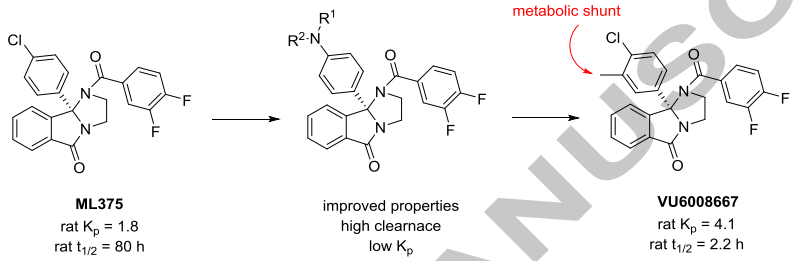

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Continued optimization of the M_5 NAM ML375: Discovery of VU6008667, an M_5 NAM with high CNS penetration and a desired short half-life in rat for addiction studies

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ABSTRACT

This letter describes the continued optimization of M_5 NAM ML375 (VU0483253). While a valuable *in vivo* tool compound, ML375 has an excessively long elimination half-life in rat ($t_{1/2}$ = 80 hours), which can be problematic in certain rodent addiction paradigms (e.g., reinstatement). Thus, we required an M_5 NAM of comparable potency to ML375, but with a rat $t_{1/2}$ of less than 4 hours. Steep SAR plagued this chemotype, and here we detail aniline replacements that offered some improvements over ML375, but failed to advance. Ultimately, incorporation of a single methyl group to the 9*b*-phenyl ring acted as a metabolic shunt, providing (*S*)-**11** (VU6008667), an equipotent M_5 NAM, with high CNS penetration, excellent selectivity versus M_{1-4} and the desired short half-life ($t_{1/2}$ = 2.3 hours) in rat.

Recently, we reported on the discovery of highly selective muscarinic acetylcholine receptor subtype 5 (M_5) inhibitors (both negative allosteric modulators (NAMs), represented by ML375 (VU0483253), **1**, and VU6000181, **2**)[1,2] and an orthosteric antagonist, ML381 (VU0488130), **3**[3] (**Figure 1**). Based on these chemotypes, we also performed a ligand-based virtual screening campaign, but no highly subtype selective M_5 inhibitors were identified.[4] Pharmacological recapitulation of the strong genetic data (from M_5 knock-out mice) linking this receptor to a role in addiction[5-7] with a selective small molecule inhibitor is of great interest. Excitingly, we have now achieved that validation in models of cocaine addiction with ML375.[8] However, the excessively long elimination half-life of ML375 in rat ($t_{1/2}$ = 80 hours)[1] is problematic in the context of addiction studies involving reinstatement paradigms and washout periods. Both **2** and **3** possessed PK profiles not suitable as *in vivo* tool compounds.[2,3] Ideally, we desired an M_5 NAM with high CNS penetration and reasonable potency but with a short to moderate half-life in rat ($t_{1/2}$ < 4 hours) to further assess this novel mechanism for the treatment of addiction. Yet, these series typify the worst caveats of allosteric modulator SAR – tremendously steep SAR.[1-3,9-11] In this Letter, we detail the continued optimization of ML375 that ultimately afforded an M_5 NAM with high CNS penetration and the desired short half-life in rat useful for evaluation in rat models of drug addiction.

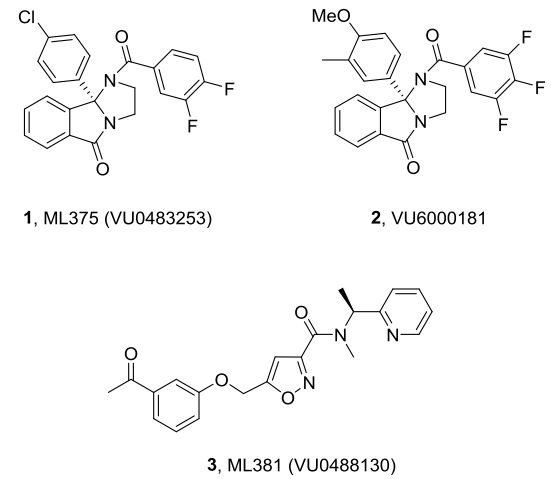


Figure 1. Structures of M_5 NAMs ML375 (**1**, VU0483253), VU6000181 (**2**) and the highly selective orthosteric M_5 antagonist ML381 (**3**, VU0488130).

As SAR to almost all portions of the ML375 scaffold resulted in largely inactive analogs (**Figure 2**), we directed our focus to further modifications to the 9*b*-phenyl moiety and explored installing aniline moieties to replace the chlorine atom. This was

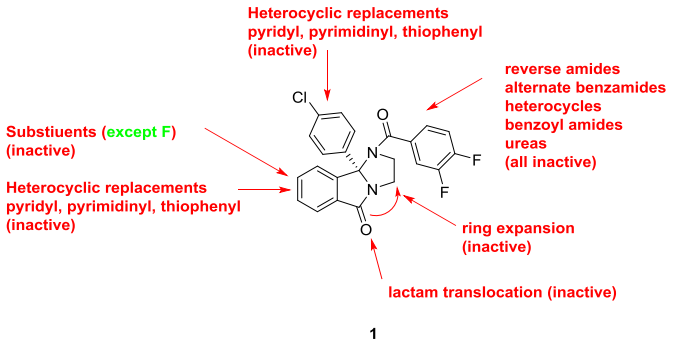
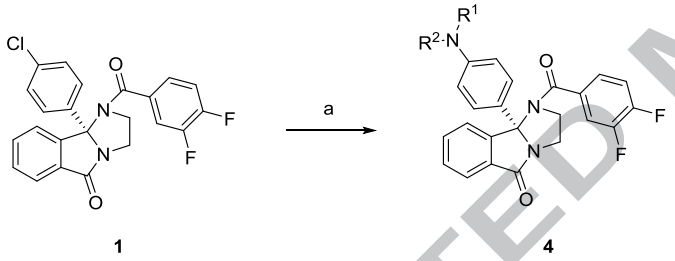


Figure 2. Summary of unproductive SAR with the M_5 NAM ML375 (**1**, VU0483253). Only fluoro substituents retained activity, but led to higher clogPs and very poor physiochemical properties.

attractive for three reasons: 1) the ability to form a salt (and hopefully improve physiochemical and DMPK properties), 2) the ease of installation onto chiral **1** (which we had in bulk) and 3) the diversity of amines for the requisite Buchwald coupling. In the event (**Scheme 1**), analogs **4** were prepared in a single step, employing a microwave-assisted Buchwald coupling in moderate to good yields (45-92%). In short order, over 100 analogs **4**

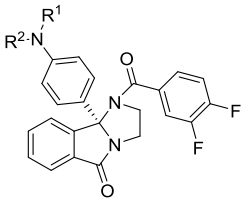
Scheme 1. Synthesis of M_5 NAM analogs **4**.[a]

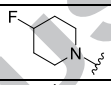
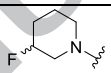
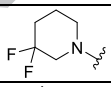
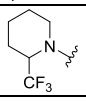
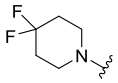
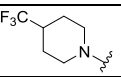
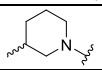
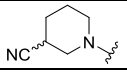
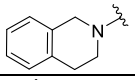
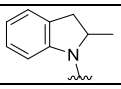
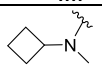
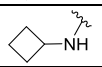
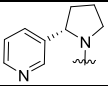
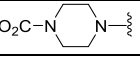


[a]Reagents and conditions: (a) HNR^1R^2 (3.0 equiv.), 5 mol% $Pd(OAc)_2$, 15 mol% SPhos, toluene (0.25 M), microwave, 20 min, 45-92%.

were synthesized, purified, and screened in our hM_5 functional assay (intracellular calcium mobilization); however, and true to the steep SAR in observed with this chemotype,[1,2] only about 10% of the analogs displayed M_5 NAM activity (**Table 1**). While none of the analogs **4** proved to more potent than **1**, several (**4d**, **4f** and **4m**) were comparable in terms of hM_5 NAM activity (hM_5 IC_{50}s in the 1.3 to 1.8 μM range and rat M_5 potency with 2-fold), but superior in terms of aqueous solubility as the respective HCl salts (cf 10 mg/mL versus <0.01 mg/mL for **1**). However, only lipophilic amine moieties provided M_5 NAMs in this subseries **4**, which resulted in high clogPs (>4), high predicted hepatic clearance (rCL_{hep} >65 mL/min/kg, hCL_{hep} >18 mL/min/kg) based on microsomal CL_{int} data, and low fraction unbound (rat and human $f_{u,plasma}$ <0.01). The series also displayed a robust *in vitro*/*in vivo* correlation (IVIVC) for clearance in rat, displaying CL_ps of >70 mL/min/kg and very short elimination half-lives ($t_{1/2}$ <30 min). Within analogs **4**, CNS distribution was variable in rat, affording brain:plasma partition coefficients (K_ps) either greater than 1, or below the limit of quantitation (no detectable brain levels). Thus, while we were excited to identify tractable SAR for this M_5 NAM chemotype and improvements in aqueous solubility, the uniformly poor disposition in rat precluded analogs **4** from further consideration as *in vivo* tools for addiction studies. Although, the improved solubility of congeners **4** should provide better tools for *in vitro* electrophysiology studies.

Table 1. Structures and activities for hM_5 NAM **1** and analogs **4.**



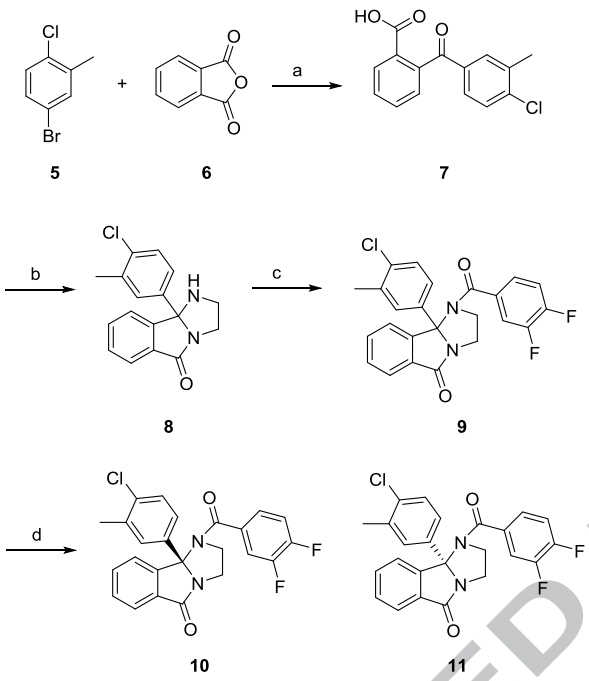
Cpd	NR^1R^2	hM_5 IC_{50} (μM)[a] [% ACh Min ±SEM]	hM_5 pIC_{50} (±SEM)[a]
1 **ML375**	"Cl"	1.11 [2.3±0.3]	5.98±0.04
4a		6.04 [10.5±2.8]	5.22±0.04
4b		4.28 [13.6±1.0]	5.37±0.04
4c		6.36 [6.9±1.7]	5.20±0.03
4d		1.46 [3.1±0.2]	5.84±0.04
4e		5.70 [2.6±0.1]	5.84±0.04
4f		1.82 [3.1±0.2]	5.74±0.04
4g		3.42 [3.2±0.2]	5.47±0.03
4h		4.01 [3.6±0.2]	5.40±0.4
4i		7.29 [26.3±6.2]	5.14±0.05
4k		8.21 [20.1±7.7]	5.11±0.10
4l		4.55 [27.0±7.7]	5.35±0.05
4m		1.32 [2.6±0.9]	5.89±0.08
4n		6.92 [25.5±9.3]	5.17±0.08
4o		3.09 [3.3±0.3]	5.52±0.05
4p		>10 [26.2±3.5]	>5
4q		3.50 [6.0±0.3]	5.46±0.03
4r		9.49 [7.5±2.4]	5.06±0.14

[a]Mean of three independent determinations performed in triplicate via an intracellular calcium mobilization assay with recombinant hM_5 cells in the presence of an ACh EC_{80}.

At this point, and with over 600 analogs synthesized and assayed in the ML375 series, it was not immediately clear where to go in the optimization effort to provide a short half-life analog

of **1**. The M_5 NAM **2**, harboring a 9*b*-(4-methoxy-3-methylphenyl) moiety, was of comparable potency to **1**, but demonstrated poor rat PK ($t_{1/2}$ <30 min, CL_p >70 mL/min/kg), as well as limited CNS penetration.[1,2] Thus, we postulated that a hybrid of NAMs **1** and **2**, with incorporation of a 3-methyl group into the 9*b*-phenyl ring of **1**, might engender a metabolic shunt, and thus provide a balance between M_5 NAM activity, physiochemical properties and disposition (i.e., reduced rat $t_{1/2}$).

Scheme 2. Synthesis of M_5 NAM analogs **9-11**.[a]



[a]Reagents and conditions: (a) nBuLi, THF, -78 °C, 2h, 50%; (b) ethylenediamine, pTsOH, 4Å sieves, toluene, 150°C μW 25 min, 70%; (c) 3,4-difluorobenzoyl chloride, DIPEA, DCM, 80%; (d) SFC, (CHIRALPAK IE, 20 mm × 250 mm column at 40 °C, back-pressure regulated at 100 bar, IPA cosolvent, 30% isocratic prep over 7 min at 80 mL/min).

The synthesis of the 9*b*-(4-chloro-3-methylphenyl)-containing M_5 NAM was straightforward (**Scheme 2**).[1,12] Lithium-halogen exchange on **5**, and addition of anhydride **6** affords benzoic acid **7** in 37% yield. Condensation with ethylenediamine, under microwave irradiation, provides the 1,2,3,9*b*-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one core **8** in 70%. Finally, acylation with 3,4-difluorobenzoyl chloride delivers racemic **9**. Chiral resolution by super criterial fluid chromatography gave (*R*)-**10** and (*S*)-**11**.[1,12] Racemic **9** was indeed an M_5 NAM (IC_{50} = 1.8 μM, pIC_{50} = 5.75±0.03, 2.9±0.29 % ACh min). As has held true for this series, the (*R*)-enantiomer **10** was devoid of M_5 NAM activity (IC_{50} >10 μM), while the (*S*)-enantiomer **11** (human M_5 IC_{50} = 1.2 μM, pIC_{50} = 5.93±0.02, 2.3±0.03 % ACh min and rat M_5 IC_{50} = 1.6 μM, pIC_{50} = 5.78±0.02, 2.6±0.03 % ACh min) was the active enantiomer (**Figure 3A**), and equipotent to **1**. Moreover, **11** (VU6008667) was selective for M_5 over M_{1-4} (**Figure 3B**). Next, we sought to assess if incorporation of a putative metabolic shunt into the framework of **1**, with **11**, would lower the 80 hour half-life in rat.

The *in vitro* DMPK profile of **11** was similar to **1** in terms of plasma protein binding ($f_{u,plasma}$ rat = 0.014,human = 0.006) and rat brain homogenate binding ($f_{u,brain}$ = 0.003), but the predicted hepatic clearance, as we had hoped, was an order of magnitude higher (rat CL_{hep} = 67 mL/min/kg and human CL_{hep} = 15 mL/min/kg). Moreover, **11** was highly brain penetrant (K_p = 4.1, $K_{p,uu}$ = 0.88). In a rat IV (1 mg/kg)/PO (3 mg/kg, solution dose) PK study, **11** displayed the desired diminished elimination half-life ($t_{1/2}$ = 2.3 hr) driven by a smaller (yet still large) volume (V_{ss} = 7.4 L/kg) and higher clearance (CL_p = 82 mL/min/kg), with moderate oral bioavailability (17% F). These results reveal a

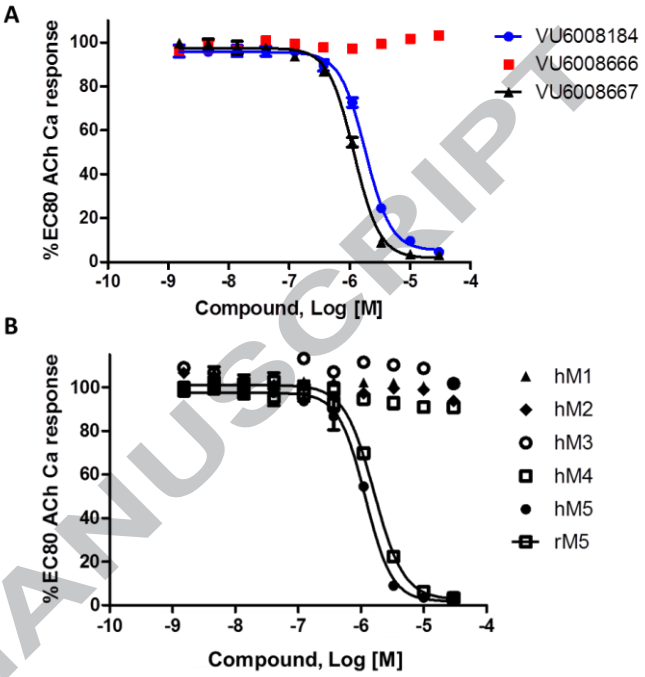


Figure 3. Molecular pharmacology profile of M_5 NAMs 9-11. A) hM_5 concentration response curves (CRCs) for **9**, **10** and **11**; B) mAChR CRCs for hM_{1-5}, highlighting the exquisite selectivity for (*S*)-**11** as an M_5 NAM, as well as rat M_5, showing no significant species differences. Data represent means from at least three independent determinations performed in triplicate via intracellular calcium mobilization assays in recombinant Chinese Hamster Ovary (CHO) cells stably transfected with the individual mAChRs.

dramatic impact of the addition of a single methyl group to **1** as a metabolic shunt, decreasing rat $t_{1/2}$ by ~35-fold while maintaining M_5 NAM potency and favorable CNS penetration. Again, an M_5 NAM with this PK profile was key for addiction studies in rat examining reinstatement paradigms and washout, where **1** could be problematic.

In summary, the continued optimization of the long half-life M_5 NAM ML375 resulted in the discovery of (*S*)-**11** (VU6008667), an equipotent human and rat M_5 NAM with a desired short half-life in rat ($t_{1/2}$ = 2.3 hr). For many of the addiction studies underway on our labs, a short half-life M_5 NAM was required. New studies are underway to directly compare ML375 to (*S*)-**11** in a variety of paradigms and with multiple drugs of abuse, and results will be reported in due course.

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12. Preparation of **12** (VU6008667): To a stirring solution of 4-bromo-1-chloro-2-methyl-benzene **5** (4.92 mL, 37.1 mmol) in THF (75 mL) cooled to -78 °C was added *n*-butyllithium (14.9 mL, 37.1 mmol) dropwise. The solution was stirred at -78 °C for 30 min and then was added to a stirring solution of phthalic anhydride **6** (5.00 g, 33.8 mmol) in THF (90 mL) at -78 °C. The reaction was stirred at -78 °C for 2 hrs before being quenched with 1N HCl (100 mL). The solution was allowed to warm to rt, the layers were separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were passed through a phase separator and concentrated. The crude material was purified using Teledyne ISCO Combi-Flash system (solid loading, 40G column, 40-80% EtOAc, 20 min run) to give 2-(4-chloro-3-methyl-benzoyl)benzoic acid **7** (4.67 g, 50.4% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (d, *J* = 7.8 Hz, 1H), 7.68 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.64-7.62 (m, 1H), 7.59 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.39-7.35 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 170.1, 136.8, 135.7, 133.6, 131.8, 131.7, 131.2, 131.1, 129.9, 129.6, 128.5, 127.9, 127.8, 20.3. To a solution of 2-(4-chloro-3-methyl-benzoyl)benzoic acid **7** (175.0 mg, 0.640 mmol) in toluene (1.59 mL) in a microwave vial was added ethylenediamine (0.09 mL, 1.27 mmol) followed by *p*-toluenesulfonic acid (8.48 mg, 0.040 mmol). The reaction subjected to microwave irradiation at 150 °C for 30 min. The reaction was diluted with EtOAc (10 mL) and quenched with saturated aqueous $NaHCO_3$ (5 mL). The layers were separated and the organic layer was washed with water (2 x 5 mL). The organic layer was dried ($MgSO_4$) before concentration to dryness. The crude material was purified using Teledyne ISCO Combi-Flash system (solid loading, 24G column, 80-100% EtOAc, 18 min run) to give 9b-(4-chloro-3-methyl-phenyl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoindol-5-one **8** (135 mg , 70.9% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82-7.77 (m, 1H), 7.55-7.53 (m, 1H), 7.50-7.45 (m, 3H), 7.34-7.28 (m, 2H), 3.86-3.78 (m, 1H), 3.68-3.64 (m, 1H), 3.29-3.15 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.8, 147.8, 137.8, 136.7, 134.7, 133.0, 131.9, 130.1, 129.6, 129.0, 125.3, 124.7, 123.5, 89.3, 50.9, 41.9, 20.4. To a stirring solution of 9*b*-(4-chloro-3-methyl-phenyl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoindol-5-one **8** (1.40 g, 4.69 mmol) in DCM (46.8 mL) was added 3,4-difluorobenzoyl chloride (0.884 mL, 7.03 mmol) followed by diisopropylethylamine (2.05 mL, 11.72 mmol). The reaction was stirred for 1.5 hrs. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the layers were separated. The aqueous layer was extracted with DCM (2 x 50 mL) and the combined organic layers were passed through a phase separator and concentrated to dryness. The crude material was dissolved in DMSO and purified using the Gilson LC system (30 x 100 mm column, 55-95%, 0.1% TFA water and ACN, 10 min run, 6 runs). The desired fractions were neutralized with saturated aqueous $NaHCO_3$ and concentrated to give racemic 9*b*-(4-chloro-3-methyl-phenyl)-1-(3,4-difluorobenzoyl)-2,3-dihydroimidazo[2,1-*a*]isoindol-5-one **9** (1.66 g, 80.7% yield). The second eluting pure enantiomer **11** was separated via CO_2 supercritical fluid chromatography (CHIRALPAK IE, 20 mm × 250 mm column at 40 °C, back-pressure regulated at 100 bar, IPA cosolvent, 30% isocratic prep over 7 min at 80 mL/min) and was determined to have >98% ee by chiral HPLC analysis CHIRALPAK IE, 4.6 mm × 250 mm column at 40 °C, backpressure regulated at 100 bar, IPA cosolvent, 30% over 7 min at 3.5 mL/min). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.03 (dd, *J* = 6.4, 1.3 Hz, 1H), 7.91-7.87 (m, 1H), 7.62 (dpentet, *J* = 7.6, 1.6 Hz, 2H), 7.37-7.31 (m, 2H), 7.25-7.18 (m, 2H), 7.06-7.02 (m, 2H), 4.34 (ddd, *J* = 12.2, 7.8, 1.8 Hz, 1H), 4.01-3.93 (m, 1H), 3.79 (ddd, *J* = 9.6, 7.5, 1.8 Hz, 1H), 3.31 (ddd, *J* = 17.9, 9.9, 7.6 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.2, 167.0, 145.9, 136.9, 136.8, 135.3, 133.6, 132.0, 130.7, 129.6, 129.1, 128.7, 124.9, 124.1, 123.8, 123.3, 118.2, 118.0, 117.0, 116.8, 87.5, 52.4, 39.8, 20.7. Specific Rotation $[\alpha]^{23}_{D}$ = -147.2° (c = 1.00, $CHCl_3$).