A Reductive Alkylation Procedure Applicable to Both Solution- and Solid-Phase Syntheses of Secondary Amines

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Introduction

The emergence of combinatorial library screening strategies for drug discovery has spurred intense activity in the field of solid-phase synthesis.[1] The ability to automate solid-phase syntheses, coupled with hyperentropic utility, the use of excess soluble reagents to drive reactions to completion, and the ready purification of resin-bound material[2] combine to make solid-phase synthesis the method of choice for combinatorial library generation. Secondary amines are important pharmacophores in many biologically active substances. Consequently, the monoalkylation of a primary amino group is an important transformation in organic synthetic chemistry. Secondary amines are typically synthesized via reductive alkylation of a primary amine with an aldehyde or ketone in the presence of a reducing agent (e.g., $NaCNBH_3$); however, overalkylation readily occurs and is of major concern.[3] Solution-phase strategies circumvent overalkylation by using less than 1 equiv of the carbonyl component relative to amine. However, this strategy is not ideal for reductive alkylation of a resin-bound amine since it necessarily results in less than quantitative yields of the desired secondary amine.

A number of solid-phase reductive alkylation protocols have been described in the literature ($NaCNBH_3$ in 1% HOAc/DMF or $NaHB(OAc)_3$).[4] In our hands, overalkylation to the tertiary amine was routinely observed when sterically undemanding aldehydes were used with these methods.[5] We have recently reported the facile formation of imines on a solid support using trimethyl orthoformate (TMOF) as the solvent.[6] In this paper, we describe a reductive alkylation procedure that provides high yields of secondary amines utilizing a large excess of carbonyl component and reducing agent in TMOF that is applicable to both solution- and solid-phase syntheses.

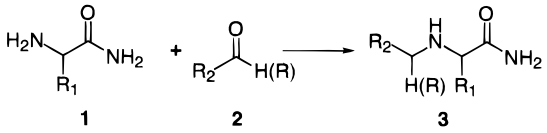
Results and Discussion

Reductive alkylations were initially studied in solution using phenylalaninamide as the amine component and a variety of aldehydes representing a range of steric and electronic characteristics (Table 1).

Table 1. Secondary Amine Synthesis via Reductive Alkylations of Primary Amines with Aldehydes and Ketones

no.	amine **1**	carbonyl **2**	isolated yield (%)
3a	H-Phe-NH_2:	propionaldehyde	77[a]
3b	$R_1 = CH_2(C_6H_5)$	isobutylaldehyde	69
3c		trimethylacetaldehyde	80
3d		benzaldehyde	74
3e		acetone	82
3f		cyclohexanone	83
3g	H-Val-NH_2: $R_1 = CH(CH_3)_2$	trimethylacetaldehyde	82[a]
3h	H-Phe-Phe-[resin]	propionaldehyde	61
3i		isobutylaldehyde	84[b]
3j		benzaldehyde	75
3k	H-Val-Phe-[resin]	trimethylacetaldehyde	72[b]

[a] Yield after standard aqueous workup. [b] Yield after HPLC purification.



(1)

Reductive alkylation with a large excess of propionaldehyde (10 equiv) and $NaCNBH_3$ (15 equiv) in neat TMOF yielded *N*-propyl-L-phenylalaninamide (**3a**) in 77% isolated yield with no evidence of overalkylated material observed by HPLC or mass spectral analysis. With the sterically hindered aldehydes isobutyraldehyde and trimethylacetaldehyde, identical conditions yielded a mixture of starting material and monoalkylated product. A dramatic improvement in isolated yields was obtained when the imine was preformed by combining phenylalaninamide and aldehyde for 30 min prior to addition of $NaCNBH_3$ (69% for isobutyraldehyde **3b** and 80% for trimethylacetaldehyde **3c**). Reductive alkylation of sterically demanding amines with bulky aliphatic aldehydes can also be achieved using these conditions as evidenced by the 82% yield obtained when valinamide was alkylated with trimethylacetaldehyde **3g**.

Attempts to alkylate phenylalaninamide with benzaldehyde yielded only starting material after workup even when imine formation was completed before addition of $NaCNBH_3$. Rationalizing that the benzylimine intermediate was too stable to be reduced under these conditions, the reaction was repeated in the presence of 1% HOAc to generate an iminium ion, which should be readily reduced. This was indeed the case, and *N*-benzyl-L-phenylalaninamide (**3d**) was obtained under these conditions with an isolated yield of 74%. This procedure has been successfully extended to the alkylation of phenylalaninamide with simple ketones in high yields (**3e** from acetone 82%; **3f** from cyclohexanone 83%).

In general, solution-phase reductive alkylations may be divided into three general classes. Unhindered aliphatic aldehydes simply require $NaCNBH_3$ in TMOF; hindered aliphatic aldehydes require premixing of the amine and aldehyde in TMOF followed by $NaCNBH_3$ addition; and aromatic aldehydes require premixing with the amine component followed by $NaCNBH_3$ addition in the presence of 1% HOAc. Experimentally, this is reduced to two procedures as hindered and unhindered aliphatic aldehydes may be treated identically.

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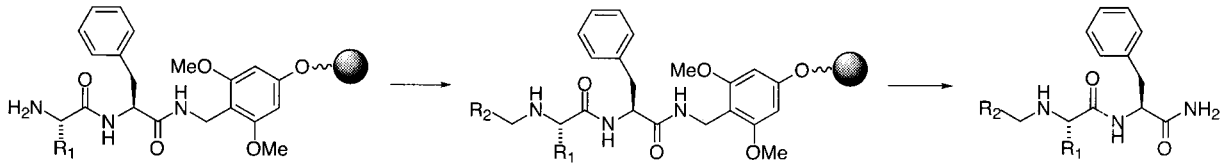
Scheme 1



We next investigated the reductive alkylation on a solid support using amino acid dimers containing phenylalanine at the carboxy terminus (Scheme 1).

Alkylation of Phe-Phe dimer with propionaldehyde in neat TMOF yielded, upon cleavage and HPLC purification, 61% of the *N*-propyl dimer **3h**. Reductive alkylations with isobutyraldehyde were incomplete even when prolonged imine formation time intervals were used, in contrast to the results obtained in solution (see **3b**), while addition of HOAc to the reaction mixture resulted in overalkylation. This problem was overcome by adding 1% MeOH as the proton source to the reductive alkylation mixture, yielding the desired *N*-isobutyl dimer **3i** in 84% yield. Similar to the solution-phase reaction, alkylation with benzaldehyde required 1% HOAc and yielded 75% of the *N*-benzyl dimer **3j**. Attempted monoalkylation of the Gly-Phe dimer with alkyl aldehydes was unsuccessful, yielding a mixture of secondary and tertiary amines. Reductive alkylation of the sterically demanding Val-Phe dimer with bulky trimethylacetaldehyde in 1% HOAc yielded the *N*-neopentyl-Val-Phe dimer **3k** in 72% yield. Thus, solution phase conditions could be extended to the solid phase with the difference that for hindered aliphatic aldehydes, premixing as well as a mild proton source (i.e., MeOH) are required.

The successful monoalkylation of primary amino groups obtained using this procedure may be attributed to the fact that the reductive potential of imines can be attenuated by varying the proton source present during the reduction with $NaCNBH_3$. This is possible because imine formation occurs in TMOF irrespective of the presence of an acid catalyst. Depending upon the steric encumbrance or electronics of the imine, the reductive potential can be attenuated by using either MeOH or HOAc as the exogenous proton source. With the procedures described in the literature,[4] manipulation of an imine's reactivity by varying the proton source was unsuccessful presumably because HOAc is required to catalyze imine formation as well as to generate an imminium ion.

In summary, we have described methodology that enables the monoalkylation of amines with various aldehydes and ketones covering a wide range of steric and electronic characteristics. The procedure has been shown to work in both solution and on a solid support. This procedure should find broad application in syntheses requiring the formation of secondary amines. Application of this work to the generation of various synthetic combinatorial libraries is ongoing and will be reported in due course.

Experimental Section

General Procedures. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. PAL-TM support (for peptide amides) was purchased from Millipore. ^{1}H-NMR spectra were determined at 400 MHz and ^{13}C-NMR at 101 MHz. Mass spectral data were obtained by electrospray mass spectroscopy. Elemental analyses were performed at the University of California, Berkeley, CA.

***N*-Propyl-L-phenylaninamide·TsOH (3a).** To phenylalaninamide (0.250 g, 1.52 mmol) dissolved in trimethyl orthoformate (20 mL) under argon was added propionaldehyde (1.1 mL, 15.2 mmol) followed by $NaCNBH_3$ (0.478 g, 7.61 mmol) dissolved in trimethyl orthoformate (20 mL). After 1 h the reaction mixture was cooled to 0 °C, quenched with 2% aqueous HCl (50 mL), and washed with ether (25 mL × 3). The ether phase was extracted with 2% aqueous HCl (25 mL × 2), and the aqueous phases were combined, cooled to 0 °C, treated with concentrated NaOH until basic, and then extracted with ether (25 mL × 4). The ether phase was dried over $MgSO_4$ and filtered. The filtrate was treated with *p*-toluenesulfonic acid (1.672 mmol) dissolved in ether (10 mL) and then placed in the freezer. The precipitate was collected by vacuum filtration, washed with ether, and dried under vacuum to provide **3a** as a colorless solid (0.441 g, 77%). ^{1}H-NMR (CD_3OD) δ: 7.72 (d, J = 8 Hz, 2H), 7.28 (m, 7H), 4.07 (m, 1H), 3.22 (m, 1H), 3.10 (m, 1H), 2.91 (m, 2H), 2.37 (s, 3H), 1.73 (m, 2H), 0.97 (t, J = 7 Hz, 3H). ^{13}C-NMR (CD_3OD) δ: 170.8, 143.6, 141.9, 135.6, 130.7, 130.1, 128.9, 127.1, 62.9, 49.7, 37.9, 21.5, 20.8, 11.3. MS (MH^+, m/z): 206. Anal. Calcd for $C_{19}H_{26}N_2O_4S\cdot0.2H_2O$: C, 59.71; H, 6.98; N, 7.33. Found: C, 59.31; H, 6.96; N, 7.42.

***N*-Isobutyl-L-phenylalaninamde·TsOH (3b).** To phenylalaninamide (0.255 g, 1.55 mmol) dissolved in trimethyl orthoformate (20 mL) under argon was added isobutyraldehyde (1.4 mL, 15.4 mmol) followed by $NaCNBH_3$ (0.487 g, 7.75 mmol) dissolved in trimethyl orthoformate (20 mL). After 1 h, the reaction was worked up as described above for **3a** to yield **3b** as a colorless solid (0.420 g, 69%). ^{1}H-NMR (CD_3OD) δ: 7.72 (d, J = 8 Hz, 2H), 7.28 (m, 7H), 4.16 (m, 1H), 3.37 (m, 1H), 3.21 (m, 1H), 2.97 (m, 1H), 2.81 (m, 1H), 2.47 (s, 3H), 2.11 (m, 1H), 1.12 (t, J = 7 Hz). ^{13}C-NMR (CD_3OD) δ: 170.7, 143.6, 141.9, 135.6, 130.7, 130.1, 130.0, 128,9, 127.1, 63.5, 55.4, 37.7, 27.4, 21.4, 20.6, 20.3. MS (MH^+, m/z): 221. Anal. Calcd for $C_{20}H_{28}N_2O_4S\cdot0.2H_2O$: C, 60.63; H, 7.24; N, 7.07. Found: C, 60.32; H, 7.30; N, 7.20.

***N*-(2,2-Dimethylpropyl)-L-phenylalaninamide·TsOH (3c).** To phenylalaninamide (0.125 g, 761 μmol) dissolved in trimethyl orthoformate (10 mL) under argon was added trimethylacetaldehyde (0.83 mL, 7.64 mmol) followed by $NaCNBH_3$ (0.245 g, 3.89 mmol) dissolved in trimethyl orthoformate (10 mL). After 1 h, the reaction was worked up as described above for **3a** to yield **3c** as a colorless solid (0.249 g, 80%). ^{1}H-NMR (CD_3OD) δ: 7.72 (d, J = 8 Hz, 2H), 7.28 (m, 7H), 4.04 (m, 1H), 3.32 (m, 1H), 3.13 (m, 1H), 2.94 (1H), 2.68 (1H), 2.48 (s, 3H), 1.07 (s, 9H). ^{13}C-NMR (CD_3OD) δ: 170.5, 143.6, 141.9, 135.8, 130.8, 130.1, 130.0, 128.8, 127.1, 64.3, 59.8, 37.5, 31.7, 27.5, 21.5. MS (MH^+, m/z): 235. Anal. Calcd for $C_{21}H_{30}N_2O_4S$: C, 62.03; H, 7.45; N, 6.89. Found: C, 61.84; H, 7.70; N, 6.88.

***N*-Benzyl-L-phenylalaninamide·TsOH (3d).** To phenylalaninamide (0.259 g, 1.58 mmol) dissolved in trimethyl orthoformate (20 mL) under argon were added acetic acid (0.4 mL) and benzaldehyde (1.6 mL, 15.7 mmol). After 30 min $NaCNBH_3$ dissolved in trimethyl orthoformate (20 mL), was added. After 1 h the reaction was worked up as described for **3a** to yield **3d** as a colorless solid (0.501 g, 74%). ^{1}H-NMR (CD_3OD) δ: 7.72 (d, J = 8 Hz, 2H), 7.46 (m, 5H), 7.28 (m, 7H), 4.15 (s, 2H), 4.08 (m, 1H), 3.24 (m, 1H), 3.12 (m, 1H), 2.37 (s, 3H). ^{13}C-NMR (CD_3OD) δ: 170.6, 143.6, 141.8, 135.5, 132.1, 131.0, 130.9, 130.7, 130.4, 130.1, 130.0, 128.9, 127.1, 62.5, 51.5, 37.8, 21.4. MS (MH^+, m/z): 255. Anal. Calcd for $C_{23}H_{26}N_2O_4S\cdot0.3H_2O$: C, 63.95; H, 6.22; N, 6.49. Found: C, 63.80; H, 6.15; N, 6.39.

***N*-Isopropyl-L-phenylalaninamide·TsOH (3e).** To phenylalaninamide (0.252 g, 1.53 mmol) dissolved in trimethyl orthoformate (20 mL) under argon was added acetic acid (0.4 mL) followed by acetone (1.1 mL, 15.0 mmol). After 30 min, $NaCNBH_3$ (0.482 g, 7.67 mmol) dissolved in trimethyl orthoformate (20 mL) was added. After 1 h, the reaction was worked

up as described above for **3a** to yield **3e** as a colorless solid (0.477 g, 82%). ^{1}H-NMR (CD_3OD) δ: 7.72 (d, J = 8 Hz, 2H), 7.28 (m, 7H), 4.11 (m, 1H), 3.36 (m, 1H), 3.20 (m, 1H), 3.09 (m, 1H), 2.37 (s, 3H), 1.35 (d, J = 5 Hz, 3H), 1.33 (d, J = 5 Hz, 3H). ^{13}C-NMR (CD_3OD) δ: 166.7, 139.6, 137.8, 131.5, 126.7, 126.0, 125.9, 124.8, 123.1, 56.4, 47.3, 34.1, 17.4, 16.1, 14.8. MS (MH^+, m/z): 207. Anal. Calcd for $C_{19}H_{26}N_2O_4S\cdot0.5H_2O$: C, 58.88; H, 7.04; N, 7.23. Found: C, 58.68; H, 7.04; N, 7.15.

***N*-Cyclohexyl-L-phenylalaninamide·TsOH (3f).** To phenylalaninamide (0.257 g, 1.56 mmol) dissolved in trimethyl orthoformate (20 mL) under argon were added acetic acid (0.4 mL) and cyclohexanone (1.6 mL, 15.4 mmol). After 30 min, $NaCNBH_3$ (0.492 g, 7.83 mmol) dissolved in trimethyl orthoformate (20 mL) was added. After 1 h, the reaction was worked up as described above for **3a** to yield **3f** as a colorless solid (0.540 g, 83%). ^{1}H-NMR (CD_3OD) δ: 7.71(d, J = 8 Hz, 2H), 7.29 (m, 7H), 4.17 (m, 1H), 3.20 (m, 1H), 3.09 (m, 1H), 2.99 (m, 1H), 2.38 (s, 3H), 2.10 (m, 2H), 1.84 (m, 2H), 1.68 (m, 1H), 1.29 (m, 5H). ^{13}C-NMR (CD_3OD) δ: 170.80, 141.87, 135.65, 130.71, 130.06, 129.98, 128.86, 127.10, 59.82, 57.97, 38.09, 31.10, 29.93, 26.08, 25.71, 21.46. MS (MH^+, m/z): 247. Anal. Calcd for $C_{22}H_{30}N_2O_4S\cdot0.3H_2O$: C, 62.32; H, 7.29; N, 6.61. Found: C, 61.99; H, 7.42; N, 6.46.

***N*-(2,2-Dimethylpropyl)-L-valinamide·TsOH (3g).** To valinamide (0.120 g, 1.03 mmol) dissolved in trimethyl orthoformate (15 mL) under argon was added trimethyl acetaldehyde (1.1 mL, 10.1 mmol) followed by $NaCNBH_3$ (0.324 g, 5.16 mmol) dissolved in trimethyl orthoformate (15 mL). After 1 h, the reaction was worked up as described above for **3a** to yield **3g** as a colorless solid (0.304 g, 82%). ^{1}H-NMR (CD_3OD) δ: 7.71 (d, J = 8 Hz, 2H), 7.24 (d, J = 8 Hz, 2H), 3.71 (d, J = 5 Hz, 1H), 2.99 (m, 1H), 2.66 (m, 1H), 2.38 (s, 3H), 2.32 (m, 1H), 1.16, (d, J = 7 Hz, 3H), 1.07 (s, 9H), 1.05 (d, J = 7 Hz, 3H). ^{13}C-NMR (CD_3OD) δ: 169.71, 143.66, 141.85, 129.96, 127.08, 68.79, 60.85, 31.76, 30.39, 27.48, 21.44, 20.35, 17.82. MS (MH^+, m/z): 187. Anal. Calcd for $C_{17}H_{30}N_2O_4S$: C, 56.94; H, 8.45; N, 7.81. Found: C, 56.79; H, 8.60; N, 7.57.

***N*-Propyl-Phe-Phe-amide·TFA (3h).** To H_2N-Phe-Phe on PAL resin (170 mg, 0.046 mmol) suspended in trimethylorthoformate (2.0 mL) under argon was added propionaldehyde (74 μL, 1.03 mmol) and the mixture shaken for 30 min. $NaCNBH_3$ (64 mg, 1.03 mmol) dissolved in trimethyl orthoformate (1.0 mL) was added. After 10 min the resin was drained, washed with methanol and ether, and dried. The N-alkylated peptide was cleaved from the resin with 95% trifluoroacetic acid/water (3 mL) for 3 h and filtered and the resin washed with trifluoroacetic acid. After concentration of the filtrate the crude material was purified by preparative HPLC using a water/acetonitrile/trifluoroacetic acid gradient to yield **3h** as a colorless solid (13 mg, 61%). ^{1}H-NMR (CD_3OD) δ: 0.69 (t, J = 7.5 Hz, 3H), 1.34 (m, 2H), 1.69 (ddd, J = 6.3, 9.1, 11.8 Hz, 1H), 2.22 (ddd, J = 5.8, 9.2, 11.8 Hz, 1H), 2.51 (dd, J = 11.6, 14.0 Hz, 1H), 2.80 (dd, J = 10.8, 12.4 Hz, 1H), 3.07 (dd, J = 4.8, 12.6 Hz, 1H), 3.17 (dd, J = 4.1, 14.0 Hz, 1H), 3.82 (dd, J = 4.8, 10.8 Hz, 1H), 4.54 (dd, J = 4.1, 11.6 Hz, 1H), 7.09−7.31 (m, 10H). ^{13}C-NMR (CD_3OD) δ: 11.3, 20.5, 23.7, 37.9, 39.2, 55.3, 62.9, 128.0, 129.0, 129.5, 130.1, 130.2, 130.3, 130.4, 135.1, 138.5, 167.7, 174.6. FAB HRMS: calcd for $C_{21}H_{28}N_3O_2$ (MH^+) 354.2182, found 354.2189.

***N*-(2-Methylpropyl)-L-Phe-Phe-amide·TFA (3i).** To H_2N-Phe-Phe on PAL resin (190 mg, 0.051 mmol) suspended in trimethyl orthoformate (2.0 mL) under argon was added isobutyraldehyde (94 μL, 1.03 mmol) and the mixture shaken for 30 min. $NaCNBH_3$ (64 mg, 1.03 mmol) dissolved in trimethyl orthoformate (1.0 mL) was added. After 10 min the reaction was worked up as described above for **3h** to yield **3i** as a colorless solid (21 mg, 84%). ^{1}H-NMR (CD_3OD) δ: 0.86 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H), 1.79 (m, 1H), 1.93 (dd, J = 7.8, 12.2 Hz, 1H), 2.42 (dd, J = 5.9, 12.2 Hz, 1H), 2.73 (dd, J = 12.1, 14.0 Hz, 1H), 3.13 (m, 3H), 3.89 (dd, J = 5.9, 9.4 Hz, 1H), 4.72 (dd, J = 4.6, 10.6 Hz, 1H), 7.18−7.35 (m, 10H). ^{13}C-NMR (CD_3OD) δ: 20.1, 20.5, 27.3, 37.8, 39.2, 55.0, 55.5, 63.5, 128.1, 129.0, 129.6, 130.2, 130.4, 130.5, 135.2, 138.4, 167.8, 174.5. FAB HRMS: calcd for $C_{22}H_{30}N_3O_2$ (MH^+) 368.2338, found 368.2340.

***N*-Benzyl-Phe-Phe-amide·TFA (3j).** To H_2N-Phe-Phe on PAL resin (226 mg, 0.063 mmol) suspended in trimethyl orthoformate (2.0 mL) under argon was added benzaldehyde (65 μL, 0.63 mmol) and the mixture shaken for 30 min. $NaCNBH_3$ (40 mg, 0.63 mmol) dissolved in trimethyl orthoformate (1.0 mL) was added followed by acetic acid (30 μL). After 10 min the reaction was worked up as described above for **3h** to yield **3j** as a colorless solid (24 mg, 75%). ^{1}H-NMR (CD_3OD) δ: 2.74 (dd, J = 11.0, 14.0 Hz, 1H), 3.09 (m, 5H), 3.22 (dd, J = 9.5, 14.0 Hz, 1H), 3.30 (m, 1H), 3.55 (d, J = 12.7 Hz, 1H), 3.94 (dd, J = 6.0, 9.0 Hz, 1H), 6.98 (m, 1H), 7.44−7.01 (m, 14H). ^{13}C-NMR (CD_3OD) δ: 37.7, 39.3, 51.2, 55.4, 62.8, 128.1, 129.0, 129.6, 130.1, 130.2, 130.4, 130.5, 130.8, 131.2, 131.8, 135.1, 138.5, 167.8, 174.6. FAB HRMS: calcd for $C_{25}H_{28}N_3O_2$ (MH^+) 402.2182, found 402.2184.

***N*-(2,2-Dimethylpropyl)-Val-Phe-amide·TFA (3k).** To H_2N-Val-Phe on PAL resin (304 mg, 0.09 mmol) suspended in trimethyl orthoformate (4.5 mL) under argon was added 2,2-dimethylpropionaldehyde (98 μL, 0.9 mmol) and the mixture shaken for 30 min. $NaCNBH_3$ (57 mg, 0.9 mmol) dissolved in trimethyl orthoformate (1.5 mL) was added followed by acetic acid (50 μL). After 10 min the reaction was worked up as described above for **3h** to yield **3k** as a colorless solid (29 mg, 72%). ^{1}H-NMR (CD_3OD) δ: 0.90 (s, 9H), 0.98 (d, J = 6.9 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.90 (d, J = 12.3 Hz, 1H), 2.21 (m, 1H), 2.60 (d, J = 12.3 Hz, 1 H), 2.87 (dd, J = 11.3, 13.6 Hz, 1H), 3.20 (dd, J = 4.5, 11.3 Hz, 1 H), 3.30 (m, 1H), 3.50 (m, 1H), 7.33−7.19 (m, 5H). ^{13}C-NMR (CD_3OD) δ: 17.9, 20.2, 27.2, 31.1, 31.5, 39.5, 55.4, 60.5, 68.7, 128.1, 129.6, 130.4, 138.5, 166.8, 175.2. FAB HRMS calcd for $C_{19}H_{32}N_3O_2$ (MH^+) 334.2494, found 334.2497.

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