# The design and synthesis of nonpeptide compounds as mimics of a conformation of methionine-enkephaline

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A model for the active conformation of methionine-enkephalin containing a β-turn was derived from computer modeling. Using a *trans*-perhydronaphthalene as a structural template and a mimic of the β-turn, target compounds were designed and synthesized. Thus, a key intermediate, *trans*-3-oxo-5β-formamidomethyl-8a-phenylmethylperhydronaphthalene, was prepared by two different routes from cyclohexanone.

The addition of a methionine-like side-chain to this key intermediate was best achieved by a reaction with the anion of methyl 2-trimethylsilyl-4-methylthiobutanoate. This led to the preparation of an *exo*-tetrasubstituted double bond in high yield. Subsequent addition of tyrosine through coupling with the 5β-aminomethyl group provided the desired perhydronaphthalene mimics of met-enkaphalin.

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A l'aide d'un ordinateur, on a déduit un modèle de la conformation active de la méthionine-encéphaline contenant une hélice β. Utilisant le perhydronaphtalène-*trans* comme modèle de structure et une imitation de l'hélice β, on a proposé et synthétisé les composés cibles. Ainsi on a préparé un intermédiaire principal, l'oxo-3 formamidométhyl-5 β phénylméthyl-8a perhydronaphtalène par deux voies différentes, en partant de la cyclohexanone.

L'addition de la méthionine, comme chaîne latérale, sur cet intermédiaire principal se fait mieux par une réaction avec l'anion du triméthylsilyl-2 méthyl-4 thiobutanoate de méthyle. Ceci conduit à la préparation d'une double liaison *exo*-tétrasubstituée avec un rendement élevé. L'addition subséquente de la tyrosine à travers le couplage avec le groupe aminométhyl-5 β conduit au perhydronaphtalène désiré qui est une réplique de la mét-encéphaline.

[Traduit par le journal]

## Introduction

In the realm of compounds that act on the central nervous system to combat pain, the opiate alkaloids (for example, morphine) have been the preeminent drugs for many years. More recently, the discovery and characterization of the naturally occuring opiate receptor agonists, the enkephalins, has renewed interest in this field (1), increasing the hope that analogs of the enkephalins would lead to drugs having reduced side-effects while maintaining a high analgesic activity.

We felt that it should be possible to design nonpeptide compounds which would mimic the enkephalins, which would be less conformationally mobile and could therefore interact specifically with the enkephalin receptors. To do this it was necessary to derive a model of what we perceived to be the active conformation for the enkephalins. Many conformational studies have been published using nmr (2, 3), fluorescence (4), theoretical studies (5–7), and more recently X-ray studies (8). Some of the conformations proposed can be correlated with synthetic opiates (9, 10). However, among the many published studies which derived "active conformations" for the enkephalins there has been no real consensus. Most do agree that the tyrosine group is very important and that the molecule is bent on itself in a β-turn. The glycines are generally thought to be positioning groups and the phenylalanine aromatic system is considered to be important for activity.

We have derived a model of the bioactive conformer of enkephalins, shown in Fig. 1, based on a combination of structure–activity relationships for the enkephalins and for the opiates, computer modeling, and comparisons with the opiates. A key feature of this model is the presence of a β-turn which adds rigidity to the flexible enkephalin

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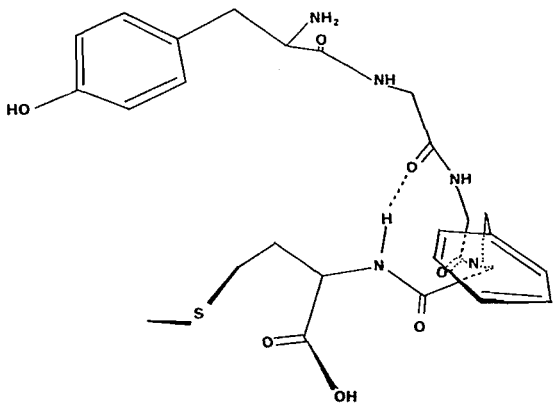


FIG. 1.

backbone and also acts as a template positioning the key groups (the tyrosine and the phenylalanine's phenyl group) in space as is found in very active opiates (e.g. morphine, etorphine). The modeling studies carried out on this conformer have revealed it to be a low energy conformer.

Using this model we sought to design novel rigid nonpeptide mimics of the enkephalins with the aid of the Merck Modeling System and the compare (superimposition) program. The β-turn in the model, with its hydrogen bond between gly$^2$ and met$^5$, makes a 10-membered ring and thus one of our most interesting structures derived by computer modeling was based on a perhydronaphthalene backbone. The perhydronaphthalene could serve to position the key groups in space as does the β-turn in the enkephalin model (Fig. 2). We therefore chose **1** as our target.

## Results and discussion

In our synthetic strategy to **1** it was considered expedient to prepare the *E* and *Z* olefin isomers, and as the addition of the tyrosine moiety to the perhydronaphthalene backbone would create diastereomers, a total of four isomers of the final

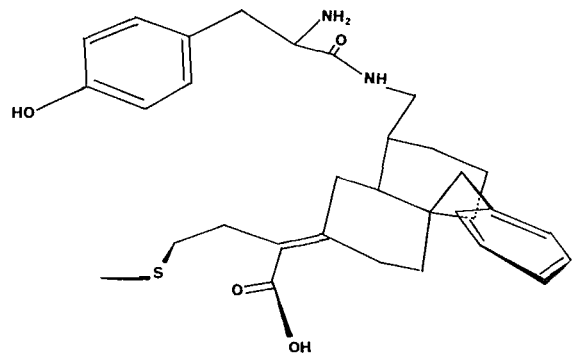
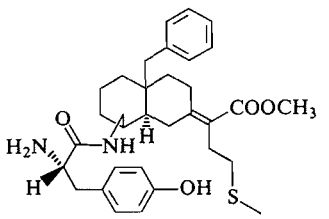


FIG. 2.

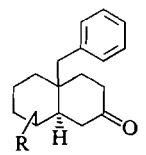
system were expected. Thus the preparation of **1** had to be achieved in as efficient and stereospecific a manner as possible. A potential difficulty was to ensure the *trans* ring junction and diaxial orientation of side chains. Strategic analysis identified the amino ketone **2***a* or a derivative such as **2***b* as key intermediates to **1**.

Compound **2***b* was prepared via two routes from cyclohexanone. The first route is outlined in Scheme 1. The key C-5 substituent was introduced via a Vilsmeier–Haack formylation reaction (11).

Cyclohexanone (**3**) was converted to 2-phenylmethylcyclohexanone (**4**) via alkylation of the pyrrolidine enamine with phenylmethylchloride following the method of Stork *et al.* (12). Subse-



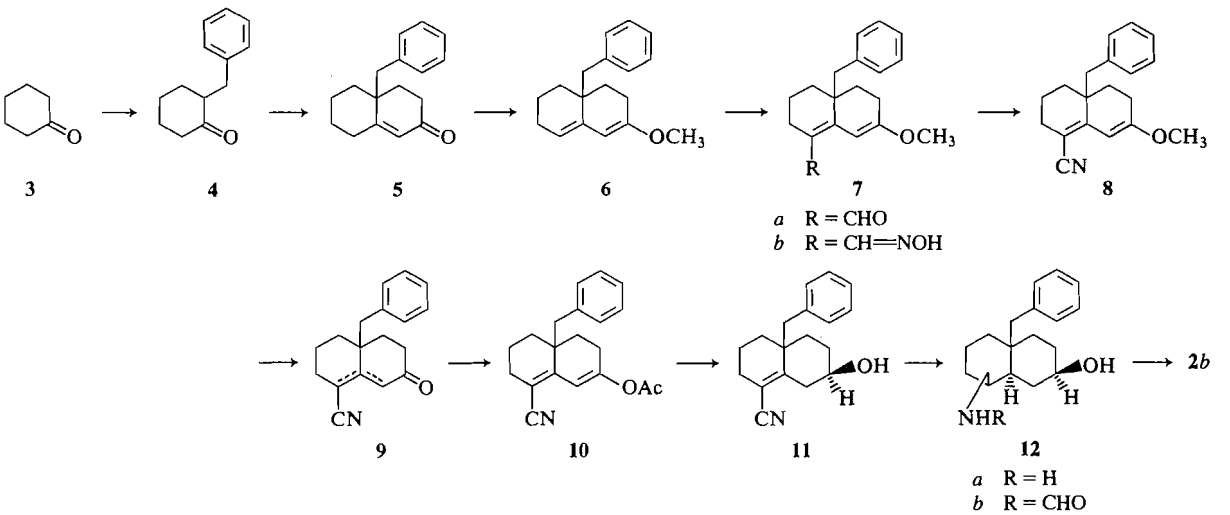
**1**



**2**

*a* R = $NH_2$
*b* R = NHCHO
*c* R = $N_3$

quent Robinson annellation (13) with methyl vinyl ketone provided 1,2,3,5,6,7,8,8a-octahydro-3-oxo-8a-phenylmethylnaphthalene (**5**). Treatment with methyl orthoformate gave the dienolether **6** which upon Vilsmeier– Haack formylation (11) provided the 5-formyl derivative **7***a* and thence the oxime **7***b* in 26% overall yield from **5** utilizing conditions similar to those developed by Yoshikoshi and co-workers (11) in their synthesis of (±) bulnesol. Thus the functionality at C(3) and C(5) were in place and it remained to introduce the required *trans* stereochemistry at the ring junction and the β-configuration at C(5). It was felt that hydrogenation of **7***b* would be nonselective whereas if a β-substituent were present at C(3), then a stereospecific reduction could be expected (14). As the oxime function led to complications in subsequent steps, it was converted to the nitrile **8** via treatment with trichloroacetonitrile (15). Hydrolysis of the enolether provided a mixture of olefinic ketones **9** which formed a single enolacetate **10**. Compound **10** was smoothly reduced by sodium borohydride to provide 5-cyano-3β-hydroxy-1,2,3,4,6,7,8,8a-octahydro-8a-phenylmethylnaphthalene (**11**). The β stereochemistry was assigned by analogy with the work of Heathcock and Kelly (16) in their β-eudesmol synthesis. Despite many trials, selective hydrogenation of the double bond could not be achieved. Hydrogenation over 10% palladium on



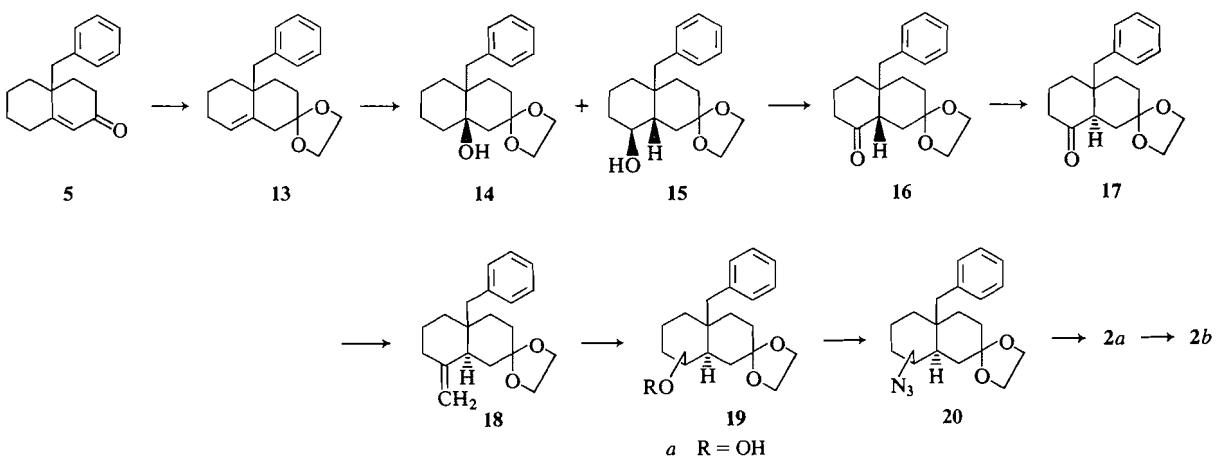

SCHEME 1

charcoal provided the aminoalcohol **12***a* contaminated with some material where the aromatic ring had been reduced. Compound **12***a* was converted to its *N*-formyl derivative **12***b* and the alcohol was oxidized with the Sarett reagent as modified by Ratcliffe and Rodehorst (17) to provide the crystalline *N*-formylketone **2***b*.

Due to the partial reduction of the aromatic ring in the hydrogenation step and also due to difficulties anticipated in scaling up the synthesis, an alternative route to **2***b* was devised and is summarized in Scheme 2.

Thus, following a scheme similar to that utilized by Marshall *et al.* (14, 18) in their synthesis of β-eudesmol, **5** was converted to the deconjugated ketal **13**. Hydroboration of **13** provided, after oxidative work-up, a mixture of *cis*-fused alcohols, **14** and **15**, plus small amounts of ketal cleavage products in a ratio of approximately 25:70:5. The desired alcohol **15** could be readily purified by chromatography or the mixture could be used as such for the subsequent oxidation ($CrO_3$·2pyr) to provide the *cis*-fused ketone **16** which, on reaction with methylenetriphenylphosphorane in the presence of excess base, first isomerized the ring junction to **17** and then effected the methylene addition. This provided the ketal olefin **18**, readily purified at this point, in 44% overall yield from **5**.

Hydroboration of **18** occurred exclusively from the α-face to provide, after oxidative work-up, the primary alcohol **19***a*, which was converted to the crystalline mesylate **19***b* (60% yield from **18**). Treatment of **19***b* with sodium azide in DMF provided the azide **20** plus the exocyclic olefin **18** in ca. 4:6 mixture. After chromatographic separation, the olefin **18** could be recycled. Reduction (LAH),



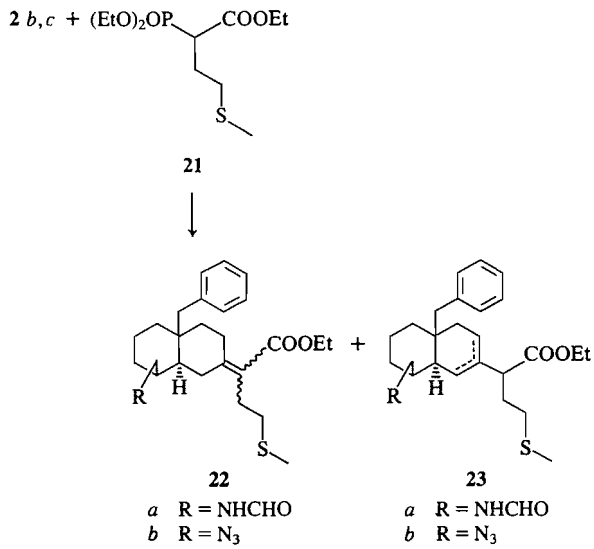

SCHEME 2

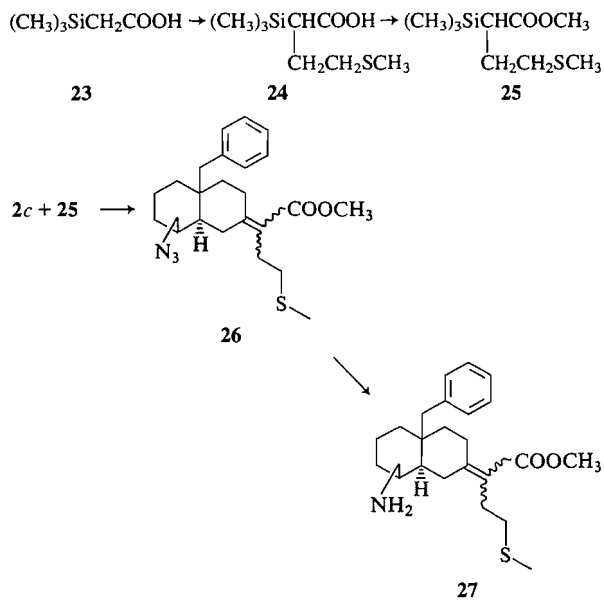
hydrolysis, and formylation of the ketal provided the *N*-formyl ketone **2***b* identical to that obtained from the previous route.

Having the required perhydronaphthalene backbone in hand, attention was directed towards the attachment of the side chain at C(3). Several possible methods were explored. Addition via a Reformatsky reaction was considered but was rapidly set aside when it was found that the dehydration of model compound proved to be nonspecific and led to mixtures of conjugated and deconjugated olefins under acidic conditions.

As it is known that endocyclic β,γ-unsaturated esters should be more stable than the exocyclic α,β-unsaturated isomers in cases such as these (19), a more specific method was sought. It was felt that the Wadsworth–Emmons phosphonate modification of the Wittig reaction (20) could provide a direct introduction of the side chain. Thus ethyl-2-diethylphosphono-4-methylthiobutyrate (**21**), readily prepared by alkylating triethylphosphonoacetate with methyl-β-chloroethyl sulfide, was found to react at best sluggishly (80–100°C, 18 h) with **2***b* or **2***c* when reacted with sodium hydride in dimethoxyethane. The mixture of *E* and *Z* adducts **22***a* or **22***b* were obtained only in rather poor yield (40–50%) and always with varying amounts of β,γ-unsaturated by-products **23***a* or **23***b*, probably due to base catalyzed isomerization of the products under these harsh conditions.

The possibility of utilizing α-trimethylsilylesters to effect the olefination was explored (21, 22). This method has not been used previously to prepare tetrasubstituted olefins but seemed worthy of investigation despite the reported failure of α,α-bistrimethylsilylesters to react with ketones (23).




SCHEME 3

As shown in Scheme 3, alkylation of the dianion of α-trimethylsilylacetic acid **23** with β-methylthioethyl chloride and subsequent esterification of **24** led to **25** in good yield. Treatment of **25** at 0°C with one equivalent of lithium diisopropylamide (LDA) followed by cooling to −78°C and addition of the azido ketone **2***c* effected a rapid and efficient (80–90% yield) reaction to provide the desired mixture of *E* and *Z* α,β-unsaturated esters **26***a*, **26***b* with no detectible traces of deconjugated by-products. The isomers were not separable at this point. Reduction of the azide was thought to be potentially a problem due to the other functionality present in the molecule. It was found that aluminium amalgam effected a clean but rather inefficient conversion of **26***a*, **26***b* to the *E* and *Z* mixture of amines **27***a*, **27***b* (42–50%). However, somewhat surprisingly, the reduction could be very cleanly effected in high yield (90%) by hydrogenation over Adams catalyst. The resultant amines could now be readily separated via column chromatography to provide the pure crystalline amines **27***a* (less polar) and **27***b* (more polar) in a 1:1 mixture.

The relative stereochemistry and ultimate proof of structure of the series was obtained via an X-ray structure determination on **27***a*, which is shown in Figure 3. Thus the less polar isomer has the *E* stereochemistry for the side chain and the more polar isomer has the *Z* stereochemistry. The rigid nature of the two cyclohexane rings with chair conformations in the *trans* perhydronaphthalene system forces the functional groups on the periphery into specific conformations. Because of a 1,3

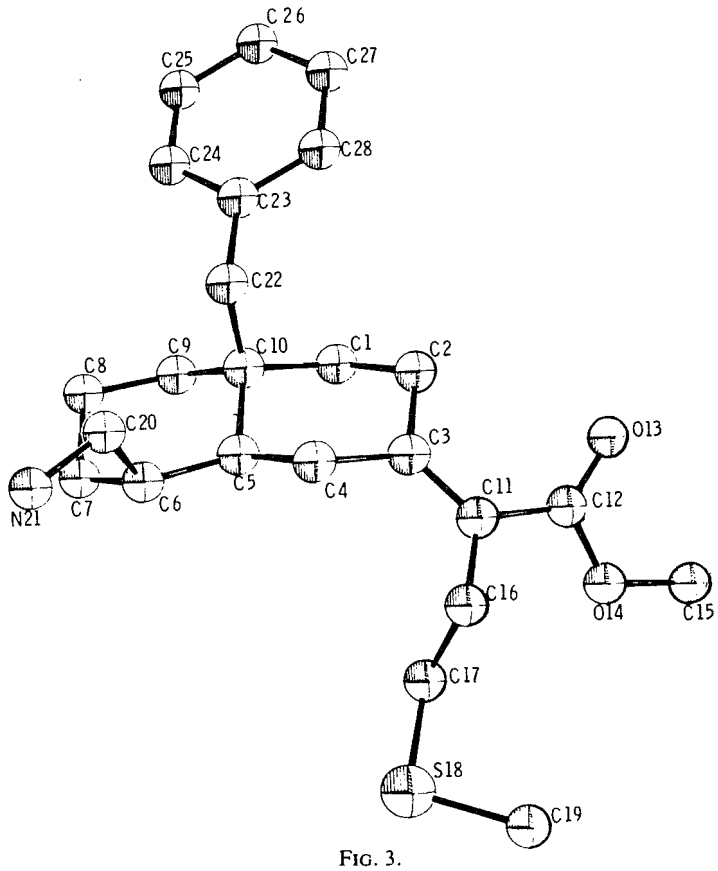



FIG. 3.

diaxial interaction C(20) and C(22) are pushed away from each other. This is clearly seen by examining the torsional angles C(8)—C(7)—C(6)—C(20) and C(10)—C(5)—C(6)—C(20) which are 79° and −77°, respectively, compared to ± 60° for an ideal chair geometry. In addition the phenyl group is forced away from the perhydronaphthalene system so that the torsional angle C(5)—C(10)—C(22)—C(23) is 176°. Also because of a nonbonded interaction between the equatorial H(2b) and O(13) the ester cannot fully conjugate with the exocyclic double bond but is twisted with a torsional angle for C(3)—C(11)—C(12)—O(13) at 37°.

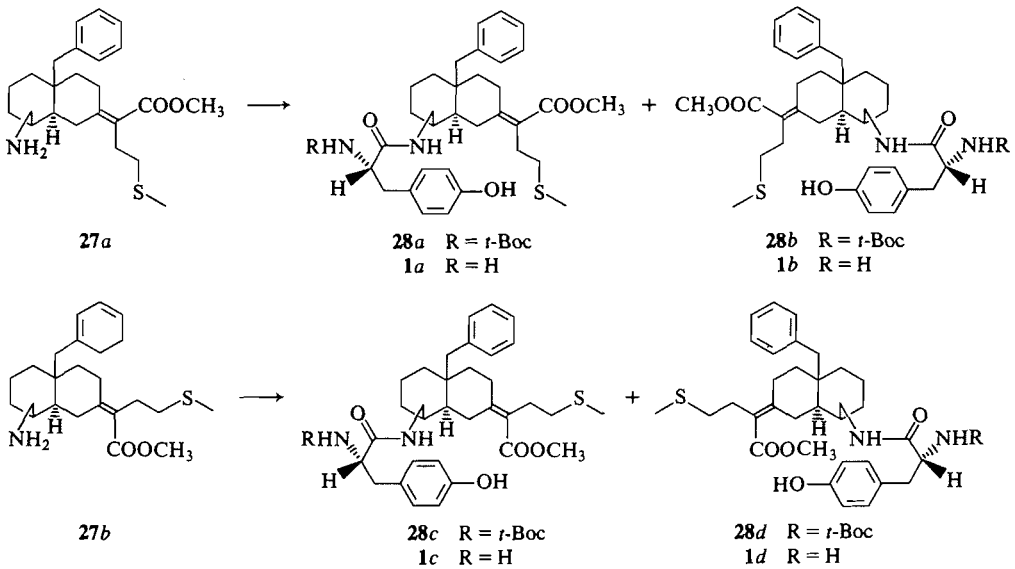
It is interesting to observe that the considerable deformation of the bond angles had been predicted by our computer modeling studies (24) but prior to determining the X-ray structure, we felt that the modeling program had exaggerated this effect.

The final conversion to the target structures was achieved via DCC coupling (25) of **27***a* and **27***b* to *N*-*t*-BOC-tyrosine to provide the *N*-protected adducts in good yields (88% and 91%, respectively) as mixtures of diastereomers. These diastereomeric pairs could be separated in each case via hplc to provide the four pure isomers **28***a*–*d*. Acid treatment in each case liberated the amino function and gave the final four isomeric target molecules directly as the hydrochloride salts **1***a*–*d*. Attempts to obtain crystalline material from these products, suitable for X-ray analysis, were unsuccessful.

These compounds have all been tested in the $^3$H-Naloxone Binding Assay (26) and, unfortunately, were found to have only weak binding activity. The possibility remains that the tyrosine side chain in these molecules does not adopt the predicted, desired conformation at the receptor site. In addition, the drastic changes done by approximating the β-turn with a perhydronaphthalene could also explain these biological results.

## Conclusion

It would therefore seem that our model has failed to accurately mimic the enkephalin active conformation. Of course activity can be affected by very subtle changes and it is possible that the steric requirements of the perhydronaphthalene unit are not tolerated by the opiate receptor. It is notable that subsequent experiments (27) have demonstrated that enkephalin derivatives where the carbonyl of the glycine 3-residue is reduced to a




methylene group have been shown to be inactive and thus it would appear that the β-turn portion of the enkephalins has significance in binding with the receptor, rather than merely acting as a template. Thus mimics such as ours which replace these hydrophilic amide bonds with more hydrophobic methylene groups may introduce an unacceptable degree of lipophilicity into this region of the receptor.

## Experimental

Melting points were taken on a Thomas Hoover apparatus in open capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 267 grating spectrophotometer. A Varian EM-360 spectrometer was used to record nmr spectra. Proton chemical shifts are relative to tetramethylsilane (TMS) as internal standard. Elemental analyses were performed by Dr. C. Daesslé of Montreal or by Galbraith and Associates, Knoxville, TN. The low resolution mass spectral analyses were performed by the Morgan–Schaffer Corporation, Montreal. A Syntex $P2_1$ automatic four-circle diffractometer was used to collect the X-ray diffraction data.

All reactions as well as column chromatography were monitored routinely with the aid of thin layer chromatography (tlc) using precoated 0.25 mm silica gel plates (Eastman Kodak) or silica gel GF plates (Analtech).

*1-Pyrrolidino-1-cyclohexene*

1-Pyrrolidino-1-cyclohexene was prepared according to the method of Stork *et al.* (12); bp 70°C/15 Torr.

*2-Benzylcyclohexanone (4)*

To 1-pyrrolidino-1-cyclohexene (238 g; 1.58 mol) dissolved in dioxane (1 L) was added benzyl chloride (277 g; 2.19 mol) and the mixture was refluxed 16 h. Water (250 mL) was then added and reflux was continued for 2.5 hours more. The dioxane was removed under vacuum and the aqueous phase was extracted four times with ether (4 × 500 mL). The combined extracts were washed with 5% aqueous hydrochloric acid (50 mL), and with water (50 mL), then dried ($Na_2SO_4$) and concentrated to an oily residue that was distilled to yield **4** (163 g; 55%), bp 105°C/0.5 Torr; ir (film) $\nu_{max}$: 1700 (C=O) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 1.2–2.6 (10H, m), 3.20 (1H, m), 7.13 (5H, s, aromatic).

*1,2,3,5,6,7,8,8a-Octahydro-3-oxo-8a-phenylmethylnaphthalene (5)*

Ketone **4** (550 g; 2.92 mol) in ether (2 L) was added to a solution of potassium hydroxide (33 g; 0.59 mol) in absolute ethanol (110 mL) maintained at 0°C. It was followed by the dropwise addition of methyl vinyl ketone (242 g; 2.92 mol) over a period of 4 hours. After warming to room temperature, water (1 L) was added and the organic layer was separated, washed with water, dried ($Na_2SO_4$), and concentrated to an oil. The residue was distilled to give 345 g (49%) of α,β-unsaturated ketone **5**, bp 155°C/0.5 Torr, which solidified on standing; mp 74–75°C; ir (KBr) $\nu_{max}$: 1660 (C=O), 1610 (C=C) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.80 (2H, s, benzylic $CH_2$), 5.72 (1H, s, H4), 7.10 (5H, s, aromatic). *Anal.* calcd. for $C_{17}H_{20}O$: C 84.95, H 8.38; found: C 85.39, H 8.49.

*5-Formyl-1,2,6,7,8,8a-hexahydro-3-methoxy-8a-phenylmethylnaphthalene (7a)*

Ketone **5** (1.06 g; 0.005 mol) was dissolved in trimethylorthoformate (7 mL) at room temperature and the solution was cooled in an ice–water bath. *p*-Toluenesulfonic acid (10 mg) was added and stirring was continued for 3 hours. Pyridine (20 mL) was added and the mixture was evaporated under high vacuum to provide crude dienol ether **6** as a brown oil which was used directly in the next reaction; $^1$Hmr ($CDCl_3$) δ: 2.80 (2H, s, benzylic $CH_2$), 3.70 (3H, s, $OCH_3$), 6.43 (1H, s, H4), 7.20 (5H, s, aromatic and H5).

Phosphorous oxychloride (0.9 mL; 9.6 mmol) was added to an ice-cooled solution of dimethylformamide (3 mL) in methylene chloride (8 mL). Dienol ether **6** from the previous reaction (1 g; crude) in methylene chloride (15 mL) was added over 15 min. The mixture was stirred at room temperature under nitrogen for 4 hours. A 20% solution of sodium acetate was added and the mixture was stirred for 30 min, then extracted with methylene chloride. The organic layers were successively washed with 10% aqueous sodium bicarbonate and with water, then dried ($Na_2SO_4$) and concentrated *in vacuo* to a brown oil, which on treatment with ether yielded crystalline **7a** (400 mg; 34% yield). Recrystallization from ether gave an analytical sample, mp 117–120°C; ir (KBr) $\nu_{max}$: 1650 (C=O), 1610 (C=C) $cm^{-1}$; $^1$Hmr

($CDCl_3$) δ: 2.87 (2H, s, benzylic $CH_2$), 3.80 (3H, s, OMe), 6.47 (1H, s, H4), 7.20 (5H, s, aromatic), 10.27 (1H, s, CHO). *Anal.* calcd. for $C_{19}H_{22}O_2$: C 80.81, H 7.85; found: C 80.68, H 7.91.

*Oxime of* 7a

The 5-formyl derivative *7a* (0.141 g; 0.5 mmol) was dissolved in methanol (4 mL) and pyridine (0.1 mL). Hydroxylamine hydrochloride (0.10 g) was added and the mixture was stirred at room temperature for 30 min. Water (10 mL) was added and the resulting oxime *7b* (0.11 g; 76%) was filtered off, washed with water, and air-dried; mp 146–147°C; ir (KBr) $\nu_{max}$: 3300 (OH), 1650 (C=N), 1620 (C=C) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.77 (2H, s, benzylic $CH_2$), 3.67 (3H, s, $OCH_3$), 5.80 (1H, s, H4), 7.20 (5H, s, aromatic), 8.43 (1H, s, —C*H*=NOH). *Anal.* calcd. for $C_{19}H_{23}NO_2$: C 76.73, H 7.80, N 4.71; found: C 76.83, H 7.73, N 4.53.

*5-Cyano-1,2,6,7,8,8a-hexahydro-3-methoxy-8a-phenylmethylnaphthalene (8)*

The oxime *7b* (600 mg; 2.02 mmol) was dissolved in trichloroacetonitrile (2 mL) and the solution was stirred at room temperature for 30 min. The mixture was stripped to dryness under high vacuum, leaving a brown oil which was taken up in $CCl_4$, filtered, and concentrated to an oil. This oil was taken up in ether, washed with 5% sodium hydroxide and with water. The organic layer was dried ($Na_2SO_4$) and evaporated to dryness to yield cyano derivative **8** (500 mg; 85% yield), mp 106–107°C; ir (KBr) $\nu_{max}$: 2210 (C≡N) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.80 (2H, s, benzylic $CH_2$), 3.72 (3H, s, OMe), 5.83 (1H, s, H4), 7.20 (5H, s, aromatic). *Anal.* calcd. for $C_{19}H_{21}NO$: C 81.68, H 7.58, N 5.01; found: C 81.71, H 7.70, N 5.08.

*Enol acetate of* ***10***

The cyano derivative **8** (184 mg; 0.66 mmol) was dissolved in tetrahydrofuran (2 mL) and concentrated hydrochloric acid (0.5 mL) was added. The mixture was stirred at room temperature for 1 hour. The mixture was taken up in methylene chloride (100 mL) and washed with water (10 mL). The organic phase was dried ($Na_2SO_4$) and concentrated to dryness to give a pale yellow oil (175 mg) which was used directly in the next reaction. Spectroscopic analysis indicated that the product **9** was largely in the enolic form; ir (film) $\nu_{max}$: 2200 (CN), 1720 (CO), 1670 (C=O conj.), 1625 (C=C) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.73 (2H, s, benzylic $CH_2$), 5.97 (1H, s, olefinic CH), 7.17 (5H, s, aromatic), 7.57 (1H, broad, OH of enol).

Compound **9** (175 mg from previous reaction) was dissolved in benzene (5 mL) and acetyl chloride (1 mL) was added, followed by the addition of triethylamine (5 drops). The mixture was kept for 28 h in the refrigerator, then was poured onto water and extracted with methylene chloride. The organic phase was dried ($Na_2SO_4$), and concentrated under vacuum to yield a yellowish oil. Purification by preparative tlc (hexane–ether 1:1 v/v) gave 0.128 g of colorless oil that crystallized on standing. Triturated in ether, **10** melted at 115–116°C; ir (KBr) $\nu_{max}$: 2050 (CN), 1765 ($OCOCH_3$), 1655 (C=C) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.17 (3H, s, OAc), 2.80 (s, 2H, benzylic $CH_2$), 6.4 (1H, m, H4), 7.2 (5H, s, aromatic). *Anal.* calcd. for $C_{20}H_{21}NO_2$: C 78.15, H 6.87, N 4.56; found: C 77.75, H 6.75, N 4.72.

*5-Cyano-3β-hydroxy-1,2,3,4,6,7,8,8a-octahydro-8a-phenylmethylnaphthalene (11)*

Enol acetate **10** (0.391 g; 1.28 mmol) dissolved in a mixture of tetrahydrofuran (8 mL), ethanol (7 mL), and water (1.5 mL) was cooled under nitrogen, to −3°C. Sodium borohydride (0.5 g) was added and the mixture was stirred overnight. A solution of 5% sodium hydroxide (2 mL) was added and the mixture was diluted with brine (20 mL) and extracted with methylene chloride (150 mL). The organic phase was washed with water, dried ($Na_2SO_4$), and evaporated to dryness. The oily residue was purified by preparative tlc (ether–hexane 7:3 v/v). Extraction of the major band yielded a colorless oil which crystallized on standing. Trituration in a small volume of ether gave 0.26 g (76%) of **11**, mp 102–104°C; ir (KBr) $\nu_{max}$: 3450 (OH); 2210 (CN), 1620 (C=C) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.87 (2H, d, benzylic $CH_2$), 3.70 (1H, broad, C*H*OH), 7.20 (5H, m, aromatic). *Anal.* calcd. for $C_{18}H_{21}NO$: C 80.86, H 7.92, N 5.24; found: C 80.79, H 8.16, N 5.27.

*3β-Hydroxy-6β-formamidomethyl-8a-phenylmethyl-*trans*-perhydronaphthalene (12*b*)*

Cyano derivative **11** (0.205 g; 0.77 mmol) was dissolved in glacial acetic acid (25 mL) and hydrogenated at 30 psi over 5% platinum on charcoal (0.133 g) for 2 hours. The catalyst was filtered off through Celite and washed with absolute ethanol (100 mL). The filtrate was concentrated *in vacuo* to yield the amino derivative **12***a* (200 mg) as a pale oil that was used for the next step; ir (film) $\nu_{max}$: 3400 (NH and OH) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.82 (2H, m, benzylic $CH_2$), 3.68 (1H, broad, CHOH), 7.18 (5H, s, aromatic).

Crude **12***a* (195 mg; 0.71 mol) dissolved in formic acid (5 mL) and acetic formic anhydride (2 mL) was heated on a steam bath for 30 min. The mixture was evaporated to dryness and taken up in methylene chloride. The resulting solution was washed with 5% sodium hydroxide, with water, dried ($Na_2SO_4$), and evaporated giving the diformyl compound (222 mg) as a pale yellow oil; ir (KBr) $\nu_{max}$: 3300 (NH), 1720 (OCHO), 1660 (NCHO) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.78 (2H, s, benzylic $CH_2$), 4.93 (1H, m, CHOCO), 7.17 (5H, s, aromatic), 8.03 (1H, s, OCHO), 8.15 (1H, s, NCHO).

The crude diformyl intermediate isolated above (0.222 g) was dissolved in methanol (5 mL) and 5% aqueous bicarbonate (2 mL) was added. The reaction mixture was stirred at room temperature for 3 hours. It was then taken up in methylene chloride and the organic phase was washed with water, dried ($Na_2SO_4$), and concentrated to give **12***b* as a pale yellow oil which solidified on standing. Trituration in ether gave 168 mg (72% from **11**) of crystalline **12***b*, mp 212–213°C; ir (KBr) $\nu_{max}$: 3300 (OH), 1660 (NCHO) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.50 (1H, d, $J$ = 14 Hz, benzylic CH), 3.00 (1H, d, $J$ = 14 Hz, benzylic CH), 3.65 (1H, broad m, =C*H*OH), 7.20 (5H, s, aromatic), 8.15 (1H, s, NCHO). *Anal.* calcd. for $C_{19}H_{27}NO_2$: C 75.71, H 9.02, N 4.65; found: C 75.41, H 9.24, N 4.89.

*6β-Formamidomethyl-3-oxo-8a-phenylmethyl-*trans*-perhydronaphthalene (2*b*)*

The hydroxy derivative **12***b* (0.15 g; 0.5 mmol) was added as a solution in dry pyridine (3 mL) to a mixture made up by adding chromium trioxide (0.5 g) to a solution of pyridine (0.8 mL) in methylene chloride (30 mL). The mixture was stirred at room temperature under nitrogen for 2 hours. The methylene chloride solution was decanted off from the brown gum which had deposited. The gum was washed with methylene chloride (6 × 50 mL) and the combined extracts were washed with 5% sodium hydroxide, water, dried ($Na_2SO_4$), and evaporated to dryness to yield a residue that was purified by preparative tlc (ether–methanol 95:5 v/v) to give pure **2***b*, mp 193–195°C (0.12 g; 81%) after trituration with ether; ir (KBr) $\nu_{max}$: 3300 (NH), 1710 (C=O), 1665 (NHCHO) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.83 (2H, s, benzylic $CH_2$), 6.35 (1H, broad, —N*H*CHO), 7.23 (5H, s, aromatic), 8.20 (1H, s, —NHC*H*O). *Anal.* calcd. for $C_{19}H_{25}NO_2$: C 76.21, H 8.41, N 4.68; found: C 76.00, H 8.64, N 4.65.

*3-Ethylenedioxy-1,2,3,4,6,7,8,8a-octahydro-8a-phenylmethylnaphthalene (13)*

Ketone **5** (50 g; 0.208 mol) was refluxed in benzene (1 L) with ethylene glycol (50 mL) and *p*-toluenesulfonic acid monohydrate (1 g) for 18 h under a Soxhlet containing calcium hydride.

The solution was washed with water (500 mL), 1 *N* sodium hydroxide (100 mL), water (500 mL), dried ($Na_2SO_4$), and concentrated. The residue was taken up in ether (50 mL) and left to crystallize. The resulting crystals were filtered and washed with hexane, providing 31.5 g of **13**. The mother liquors, recycled through the above procedure, yielded a further 14.7 g for a total yield of 46.2 g (77%), mp 91–93°C; $^1$Hmr ($CDCl_3$) δ: 2.80 (2H, m, benzylic $CH_2$), 3.87 (4H, s, $CH_2CH_2$), 5.40 (1H, m, olefinic H), 7.10 (5H, s, aromatic). *Anal.* calcd. for $C_{19}H_{24}O_2$: C 80.24, H 8.50; found: C 80.47, H 8.71.

*3-Ethylenedioxy-5*β*-hydroxy-8a-phenylmethyl-*cis-*perhydronaphthalene (**15**)*

To a solution of olefin **13** (21 g; 74 mmol) in anhydrous tetrahydrofuran (100 mL) cooled at 0°C was added dropwise and under nitrogen a solution of diborane in tetrahydrofuran (150 mL of 1 *M* solution). The reaction mixture was stirred at room temperature for 3 hours. It was then cooled to 0°C and methanol (30 mL) was added slowly. Sodium hydroxide (50 mL, 1 *N*) was then added, followed by the addition of 30% hydrogen peroxide (20 mL). The excess hydrogen peroxide was destroyed by adding a solution of sodium bisulfite until no peroxide was detected by starch iodide paper. The mixture was then extracted three times with methylene chloride and the combined extracts were washed with water and dried ($Na_2SO_4$). Concentration under vacuum gave crude **15** (27.3 g) which was used as such for the next step.

A sample of the crude mixture was purified by preparative tlc (ether–hexane 70:30 v/v) to yield the desired alcohol **15** as an oil and the tertiary alcohol **14** also as an oil. The ratio of **15** to **14** was 3:1.

Secondary alcohol **15**; ir (film) $\nu_{max}$: 3450 ($OH^-$), 1604 (aromatic) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.80 (2H, s, benzylic $CH_2$), 3.93 (4H, s, ethylenedioxy protons), 7.17 (5H, s, aromatic).

Tertiary alcohol **14**; ir (film) $\nu_{max}$: 3520 (OH), 1601 (aromatic) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.83 (1H, d, $J$ = 14 Hz, benzylic CH), 3.13 (1H, d, $J$ = 14 Hz, benzylic CH), 4.00 (4H, s, ethylenedioxy protons), 7.17 (5H, s, aromatic).

*3-Ethylenedioxy-5-oxo-8a-phenylmethyl-*cis-*perhydronaphthalene (**16**)*

Crude **15** (27.3 g; 0.09 mol) dissolved in acetone (500 mL) was oxidized by adding slowly 55 mL of 1.15 *M* Jones reagent (28). After stirring at room temperature for 30 min, ether (250 mL) was added. The two layers were separated and the organic layer was washed with dilute sodium hydroxide and with water, dried ($Na_2SO_4$), and concentrated to a residue that solidified on standing (26.2 g). The crude **16** was used as such in the following step.

A 200 mg sample was purified by preparative tlc (ether–hexane 1:1 v/v). Recrystallized from methanol, pure *cis*-**16** had mp 117–118°C; ir (KBr) $\nu_{max}$: 1705 (C=O), 1602 (aromatic) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.57 (2H, AB quartet, $J_{A,B}$ = 14 Hz, benzylic $CH_2$), 3.84 (4H, s, ethylenedioxy protons), 7.17 (5H, s, aromatic). *Anal.* calcd. for $C_{19}H_{24}O_3$: C 75.97, H 8.05; found: C 76.24, H 8.24.

*3-Ethylenedioxy-5-oxo-8a-phenylmethyl-*trans-*perhydronaphthalene (**17**)*

Purified *cis*-ketone **16** (670 mg; 2.2 mmol) and sodium methoxide (100 mg) in methanol (20 mL) were refluxed under nitrogen for 2.5 hours. The mixture was poured into water (10 mL), extracted with chloroform (3 × 10 mL), washed with brine, dried ($Na_2SO_4$), and evaporated to dryness. The residue was chromatographed on preparative tlc (ether–hexane 70:30 v/v) to yield the *trans* isomer **17** (440 mg) and the *cis* isomer **16** (180 mg). Recrystallized from methanol, the *trans* isomer **17** had mp 119–120°C; ir (KBr) $\nu_{max}$: 1703 (C=O), 1602 (aromatic) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.57 (2H, AB quartet, $J_{A,B}$ = 14 Hz, benzylic protons), 3.97 (4H, s, ethylenedioxy protons), 7.20 (5H, m, aromatic protons). *Anal.* calcd. for $C_{19}H_{24}O_3$: C 75.97, H 8.05; found: C 75.42, H 7.84.

*3-Ethylenedioxy-5-methylene-8a-phenylmethyl-*trans-*perhydronaphthalene (**18**)*

A. *Preparation from compound **17***

*trans*-Ketone **17** (50 mg; 0.17 mmol) was added at −78°C to the ylid formed by reacting at 0°C triphenylmethylphosphonium bromide (800 mg; 2 mmol) with *n*-butyllithium (0.7 mL of 2.4 *M* solution in hexane). The mixture was stirred 15 min at −78°C and then allowed to warm to room temperature for 1 hour. It was poured into water, extracted with ether, and the organic extracts were washed with water, dried ($Na_2SO_4$), concentrated *in vacuo*, and purified by preparative tlc, eluting with ether–hexane (50:50 v/v). The resultant oil was triturated with hexane and, after recrystallization from hexane, **18** melted at 75–77°C; ir (KBr) $\nu_{max}$: 3080, 1645, and 898 (exocyclic methylene) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.60 (2H, s, benzylic $CH_2$), 3.95 (4H, s, ethylenedioxy), 4.52 and 4.83 (2H, two broad s, $=CH_2$), 7.17 (5H, s, aromatic). *Anal.* calcd. for $C_{20}H_{26}O_2$: C 80.49, H 8.78; found: C 80.51, H 8.54.

B. *Preparation from compound **16***

The crude **16** (26 g) from the previous reaction dissolved in THF (100 mL) was added over 10 min, under $N_2$, to an ice-cold solution of methylenetriphenylphosphorane (0.219 mol) (previously prepared by stirring together for 1 hour at room temperature in THF (400 mL) potassium *tert*-butoxide (29.4 g; 0.262 mol) and methyltriphenylphosphonium bromide (78.1 g; 0.219 mol)).

The reaction mixture was warmed to room temperature, then refluxed for 20 min. It was then cooled, poured into water (500 mL), and extracted with dichloromethane (3 × 250 mL). The organic layer was washed with brine (500 mL), dried ($Na_2SO_4$), and concentrated. The residue was partitioned between 400 mL of hexane and 400 mL of 75% aqueous methanol. The lower phase was washed with another 400 mL of hexane. The combined hexane layers were dried ($Na_2SO_4$) and reduced to dryness to give a residue (23.3 g) which was purified by column chromatography on silica gel. Elution with 10% ether–hexane yielded pure **18** (11.1 g; 43.5% based on **13**), mp 75–77°C.

*Mesylate of 3-ethylenedioxy-5*β*-hydroxymethyl-8a-phenylmethyl-*trans-*perhydronaphthalene (**19**a)*

Under $N_2$ atmosphere, 150 mL of 1 *M* borane in THF was added dropwise over 15 min to an ice-cold solution of *trans* olefin **18** (20.4 g; 68.4 mmol) in dry THF (100 mL). The mixture was stirred at room temperature for 1.5 hours, cooled in an ice–water bath, and 30 mL of methanol was added dropwise to decompose excess borane. Sodium hydroxide (1 *N*, 30 mL) and then 30% hydrogen peroxide (20 mL) were added, each over a period of 15 min. After stirring for 15 min at 0°C, a solution of sodium sulfite (18 g) in water (100 mL) was added dropwise to decompose excess peroxide. The mixture was extracted with methylene chloride (3 × 500 mL). The organic layer was washed with water, dried ($Na_2SO_4$), and evaporated. The crude residue was chromatographed on silica gel eluting with 2.5% methanol–chloroform, to yield **19***a* (13.6 g, 63%); ir (KBr) $\nu_{max}$: 3400 (OH), 1600 (aromatic) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.60 (2H, AB quartet; $J_{A,B}$ = 14 Hz, benzylic), 3.67 (2H, m, $—CH_2O$), 3.90 (4H, s, ethylenedioxy), 7.17 (5H, s, aromatic); *m/e*: 316 ($M^+$).

To an ice-cold solution of the alcohol derivative **19***a* (6.8 g; 21.5 mmol) in pyridine (100 mL) was added methanesulfonyl chloride (3.7 g; 32 mmol). The mixture was stored at 0°C for 3 days, then was evaporated to dryness *in vacuo* and the residue was partitioned between ether and water. The organic layer was

washed with water, dried ($Na_2SO_4$), and evaporated to provide the solid mesylate **19***b*, mp 121–126°C (8.1 g; 95%). Recrystallization from cyclohexane raised the mp to 141–143°C; ir (KBr) $\nu_{max}$: 1350, 1175 ($SO_2$) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.58 (2H, AB quartet, $J_{A,B}$ = 14 Hz, benzylic $CH_2$), 2.97 (3H, s, $OSO_2CH_3$), 3.97 (4H, s, ethylenedioxy), 4.25 (2H, m, —$CH_2O$), 7.17 (5H, s, aromatic); *m/e*: 394 ($M^+$). *Anal.* calcd. for $C_{21}H_{30}SO_5$: C 63.93, H 7.66, S 8.12; found: C 64.00, H 7.73, S 8.11.

*5β-Azidomethyl-3-ethylenedioxy-8a-phenylmethyl-*trans*-perhydronaphthalene (20)*

A mixture of mesylate **19***b* (8.5 g; 21.5 mmol), sodium azide (17 g; 262 mmol), and 100 mL of DMF was heated in an oil bath preheated to 125°C, under $N_2$ for 1 hour. The mixture was poured into water and extracted with ether. The organic layer was washed with water, dried ($Na_2SO_4$), and evaporated to give a mixture (5.8 g) which was chromatographed on silica gel, eluting with 10% ether – *n*-hexane to give regenerated olefin **18** (3.1 g; 49%) and the desired azide **20** (2.0 g; 28%), which crystallized on standing, mp 88–89°C; ir (KBr) $\nu_{max}$: 2100 ($N_3$) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.63 (2H, AB quartet, $J_{A,B}$ = 14 Hz, benzylic $CH_2$), 3.43 (2H, m, $CH_2N_3$), 3.97 (4H, s, ethylenedioxy), 7.17 (5H, s, aromatic). *Anal.* calcd. for $C_{20}H_{27}N_3O_2$: C 70.35, H 7.97, N 12.30; found: C 70.39, H 8.15, N 12.00.

*5β-Aminomethyl-3-oxo-8a-phenylmethyl-*trans*-perhydronaphthalene (2*a*)*

To a suspension of LAH (1.0 g; 26 mmol) in THF (150 mL) was added the azide **20** (3.5 g; 10.3 mmol) in THF (25 mL). After stirring under $N_2$ for 30 min at room temperature, the reaction was quenched with water (0.5 mL), 15% NaOH (0.5 mL), and water (1.5 mL). The mixture was filtered and the filtrate concentrated to yield crude 5β-aminomethyl-3-ethylenedioxy-8a-phenylmethyl-*trans*-perhydronaphthalene (3.4 g) which was taken up in methanol (150 mL), water (10 mL) and concentrated HCl (5 mL). This mixture was heated under $N_2$ for 30 min at 70°C, then stirred at room temperature for 30 min. The resultant crystals were filtered and washed with ether to yield **2***a* (3.0 g; 64% from **20**), mp 285°C (dec.); ir (KBr) $\nu_{max}$: 1710 (C=O) $cm^{-1}$; $^1$Hmr (DMSO-$d_6$) δ: 2.2–3.2 (6H, m, $CH_2$—CO—$CH_2$ and —$CH_2$—$NH_2$), 7.27 (5H, s, aromatics). *Anal.* calcd. for $C_{18}H_{25}NO.HCl$: C 70.22, H 8.51, N 4.55, Cl 11.51; found: C 69.93, H 8.88, N 4.46, Cl 11.41.

*3-Oxo-5β-formamidomethyl-8a-phenylmethyl-*trans*-perhydronaphthalene (2*b*)*

To the HCl salt **2***a* (210 mg; 0.77 mmol) in formic acid (10 mL) was added formic acetic anhydride (5 mL) and sodium bicarbonate (500 mg). The reaction mixture was refluxed overnight, then concentrated *in vacuo*, diluted with methylene chloride, washed with sodium bicarbonate, dried ($Na_2SO_4$), and concentrated *in vacuo*, to yield a residue which was purified by preparative tlc (5% methanol–chloroform). Recrystallization from methylene chloride – hexane yielded **2***b*, mp at 198–199°C.

This material, compared to the formyl derivative prepared by Scheme 1, was found to be identical and had mixture mp 197–199°C.

*5β-Azidomethyl-3-oxo-8a-phenylmethyl-*trans*-perhydronaphthalene (2*c*)*

The ketal **20** (9.5 g; 28.7 mmol) was dissolved in methanol (200 mL) and 3 *N* hydrochloric acid (50 mL) was added slowly. The mixture was stirred at room temperature for a period of 2.5 hours. The resultant crystals were filtered off to yield **2***c* (7.6 g, 89%), mp 155–157°C; ir (KBr) $\nu_{max}$: 2100 ($N_3$), 1690 (C=O) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.77 (2H, AB quartet; *J* = 14 Hz, benzylic), 3.47 (2H, m, $CH_2N_3$), 7.17 (5H, s, aromatic). *Anal.* calcd. for $C_{18}H_{23}N_3O$: C 72.70, H 7.79, N 14.13; found: C 72.90, H 7.76, N 13.91.

*Ethyl-2-diethylphosphono-4-methylthiobutyrate (21)*

Triethylphosphonoacetate (4.4 g; 20 mmol) was added slowly to a suspension of sodium hydride (0.95 g of 50% dispersion in oil) in dimethylformamide (15 mL). Methylthioethylchloride (4.4 g; 40 mmol) was then added and the resulting mixture was heated overnight at 80°C. A precipitation of sodium chloride occurred after three hours. The reaction mixture was cooled, filtered, and evaporated to dryness. The residue was then distilled to yield first unreacted triethylphophonoacetate: bp 105°C/0.5 Torr and then **21**; bp 127–135°C/0.5 Torr (2.8 g; 42% yield); ir (film) $\nu_{max}$: 1735 (C=O) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 1.37 (9H, m, $3CH_3$), 2.17 (3H, s, $SCH_3$), 2.5 (4H, m), 3.03 (1H, m), 4.2 (6H, m, $3CH_2$). *Anal.* calcd. for $C_{11}H_{23}PO_5S$: C 44.28, H 7.77, S 10.75; found: C 44.09, H 7.80, S 10.70.

*Z- and E-3-(3'-Methylthio-1'-carbomethoxypropylidin-1'-yl)-5β-formamidomethyl-8a-phenylmethyl-*trans*-perhydronaphthalene (22*a*)*:

To sodium hydride (25 mg; 50% dispersion in mineral oil, 0.54 mmol) suspended in dimethoxyethane (5 mL) at 0°C under $N_2$ was added ethyl 2-diethylphosphono-4-methylthiobutyrate (150 mg; 0.5 mmol). After stirring for 30 min, the mixture was cooled to −78°C and ketone **2***b* (30 mg; 0.1 mmol) in dimethoxyethane (2 mL) was added. The mixture was stirred at −78°C for 1 hour and then warmed to an internal temperature of 80°C for 6 hours. The mixture was poured into water and extracted with ether. The organic layer was washed with water, dried ($Na_2SO_4$), and concentrated *in vacuo* to yield a residue (197 mg) that was chromatographed on a preparative tlc plate, eluting with 2% methanol–chloroform. The product, $R_f$ = 0.2 (19 mg; 43%), was a mixture of desired **22***a* and of isomer **23***a* as could be determined by the presence of two carbonyl absorptions at 1685 $cm^{-1}$ and 1735 $cm^{-1}$ respectively in the ir spectrum.

*Z- and E-3-(3'-Methylthio-1-carbomethoxy propylidinyl)-5β-azidomethyl-8a-phenylmethyl-*trans*-perhydronaphthalene (22*b*)*:

To a suspension of sodium hydride (47 mg; 50% dispersion in mineral oil; 1 mmol) in dimethoxyethane (5 mL) at 0°C under $N_2$ was added **21** (300 mg; 1 mmol). After stirring for 30 min, ketone **2***c* (27 mg; 0.1 mmol) in DMF (1 mL) was added. The reaction mixture was heated at 80°C for 4 hours. It was then poured into water and extracted with ether. The organic layer was washed with water, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was chromatographed on a preparative tlc plate, eluting with ether–hexane 1:5 v/v to give 18 mg (41%) of a mixture of **22***b* and **23***b* as a yellowish oil. The presence of a mixture was again demonstrated by ester absorptions of equal intensity at 1730 $cm^{-1}$ and 1700$^{-1}$.

*Methyl 2-trimethylsilyl-4-methylthiobutyrate (25)*

To a solution of diisopropylamine (128 g; 1.27 mol) in anhydrous THF (1 L) cooled to 0°C was added dropwise over 20 min *n*-butyllithium (557 mL of 2.28 *M* in hexane). The mixture was stirred for 30 min at 0°C. α-Trimethylsilylacetic acid (**23**) (76.3 g; 0.58 mol) dissolved in anhydrous THF (100 mL) was then added dropwise over a period of 15 min and the resulting mixture was stirred at 0°C for 30 min. 2-Methylthioethylchloride (67 g; 0.60 mol) was then added dropwise over 15 min. The reaction mixture was refluxed for 70 h, then was cooled to room temperature and poured into 1.5 liters of water. The organic layer was removed and the aqueous layer was further washed with ether. The aqueous layer was acidified with 20% citric acid and extracted several times with ether. These ether extracts were washed with water, dried ($Na_2SO_4$), and evaporated to give a crude residue that was distilled under vacuum to provide **24**, bp 130°C/0.2 Torr (27 g; 23% yield); $^1$Hmr δ: 0.1 (9H, s,

—$SiMe_3$), 2.1 (3H, s, $SCH_3$), 10.3 (1H, b, exchanged by $D_2O$, COOH).

The acid was esterified ($CH_2N_2$, excess) in ether. The resulting solution was washed with sodium bicarbonate (5%), dried ($Na_2SO_4$), concentrated, and purified by preparative hplc (5% ether–hexane) to give 19 g (69%) of methyl-2-trimethylsilyl-4-methylthiobutyrate **25**; ir (KBr) $\nu_{max}$: 1712 $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 0.15 (9H, s, $SiMe_3$), 2.07 (3H, s, $SCH_3$), 3.67 (3H, s, $COOCH_3$). *Anal.* calcd. for $C_9H_{20}SSiO_2$: C 49.04, H 9.15, S 14.55; found: C 49.23, H 9.18, S 14.32.

*3-(3'-Methylthio-1'-carbomethoxypropylidinyl)-5β-azidomethyl-8a-phenylmethylperhydronaphthalene (**26**)*

To a solution of diisopropylamine (4.75 mL; 36 mmol) in tetrahydrofuran (100 mL) at 0°C under $N_2$ was added a 2.2 *M* solution of *n*-butyl lithium in hexane (16.36 mL; 36 mmol). The mixture was stirred at 0°C for 15 min and then cooled at −78°C. Ester **25** (8 g; 36.4 mmol) dissolved in 10 mL tetrahydrofuran was added over 5 minutes. The resulting mixture was stirred for 20 min at −78°C and then ketone **2***c* (5.23 g; 17.6 mmol) in 40 mL tetrahydrofuran was added dropwise over a period of 10 min. The reaction mixture was stirred at −78° for another 10 min, and was allowed to warm to room temperature. The mixture was poured into water and extracted with ether. The organic phase was washed successively with 3 *N* hydrochloric acid and with water, dried ($Na_2SO_4$), and evaporated to dryness to yield a pale yellow oil which was chromatographed on silica gel. Elution with 5% ether–hexane gave successively methyl ester **25** (5.2 g), and the mixture of *E* and *Z* isomers of the desired product **26** (7.2 g; 96%); ir (NaCl) $\nu_{max}$: 2100 ($N_3$), 1705 (C=O) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.13 (3H, s, $SCH_3$), 2.60 (4H, s, $CH_2CH_2$), 3.50 (2H, m, $CH_2N_3$), 3.73 (3H, s, $OCH_3$), 7.17 (5H, s, aromatic); *m/e*: 427 (weak, $M^+$), 399 (M − $N_2$), 384 (M − $HN_3$).

*Z and E Isomers of 3-(3'-methylthio-1'-carbomethoxypropylidinyl)-5β-aminomethyl-8a-phenylmethyl-*trans*-perhydronaphthalene (**27**a and **27**b)*

The *Z* and *E* mixture of azide **26** (7.5 g; 17.6 mmol) was dissolved in methanol (300 mL) and hydrogenated in a Parr hydrogenator at 30 psi for one hour over platinum oxide (500 mg). The reaction mixture was filtered through Celite and concentrated *in vacuo* to yield an oil which was chromatographed on silica gel. Elution with methanol–chloroform – aqueous ammonia (2000:40:5 v/v/v) gave the *E* isomer (3.6 g) and the *Z* isomer (3.4 g) successively (99% combined yield). The *E* isomer **27***a* recrystallized from ether gave an analytical sample, mp 96.5–97.5°C; ir (KBr) $\nu_{max}$: 1705 ($COOCH_3$), 1610, 3350 ($NH_2$) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.10 (3H, s, $SCH_3$), 2.53 (4H, s, —$CH_2CH_2S$—), 3.75 (3H, s, $OCH_3$), 7.07 (5H, s, aromatic); *m/e*: 401 ($M^+$), 386 (M − $CH_3$), 370 (M − $OCH_3$), 354 (M − $SCH_3$), 340 (base peak, M − $CH_2SCH_3$), 310 (M − $CH_2C_6H_5$). *Anal.* calcd. for $C_{24}H_{35}NO_2S$: C 71.78, H 8.78, N 3.49, S 7.98; found: C 71.89, H 8.92, N 3.42, S 7.69.

The *Z* isomer **27***b* recrystallized from ether gave an analytical sample, mp 104–106°C; ir (KBr) $\nu_{max}$: 1705 ($COOCH_3$), 1610, 3350 ($NH_2$) $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 2.10 (3H, s, $SCH_3$), 2.53 (4H, s, —$CH_2CH_2S$—), 3.73 (3H, s, $OCH_3$), 7.07 (5H, s, aromatic); *m/e*: 401 ($M^+$), 386, 370, 354, 340 (base peak), 310. *Anal.* calcd. for $C_{24}H_{35}NO_2S$: C 71.78, H 8.78, N 3.49, S 7.98; found: C 71.93, H 8.89, N 3.43, S 7.71.

*X-ray structure determination of **27**a*

Suitable crystals of **27***a* for single crystal X-ray diffraction experiments formed from ether containing traces of chloroform. Preliminary diffraction experiments indicated that the space group was *P*1 with $a$ = 11.029(4) Å, $b$ = 13.460(4), $c$ = 8.709(2), α = 97.80(2)°, β = 110.34(2), and γ = 68.78(2) for $Z$ = 2. Of the 3061 reflections collected using CuKα radiation (λ = 1.5418 Å), 2624 were observed and corrected for Lorentz and polarization effects. Application of direct methods (29) and tangent formula recycling procedures (30) provided initial coordinates for all nonhydrogen atoms. After refinements and Fourier calculations hydrogens were placed and refined. The function $\Sigma w(|F_o| - |F_c|)^2$ was minimized with full matrix least squares techniques (31) to give an unweighted residual factor of 0.077. Tables 1, 2, and 3 contain the final atomic coordinates and temperature parameters, bond distances, and bond angles, respectively.[1]

*The coupling of **27**a with* N-t-*BOC-tyrosine*

A solution of the *E* isomer **27***a* (2.63 g; 6.56 mmol), *t*-BOC tyrosine (3.72 g; 13.2 mmol), dicyclohexylcarbodiimide (2.72 g; 15 mmol), and 1-hydroxybenzotriazole (2.03 g; 15 mmol) in methylene chloride (140 mL) was stirred at room temperature overnight. The reaction mixture was diluted with ether and was then filtered. The cake was washed with ether. The combined filtrates were washed with 20% citric acid, with 5% sodium bicarbonate, and with water. After drying over sodium sulfate, the solution was evaporated to a foam (6.08 g).

The mixture of diastereoisomers was separated by chromatography on silica gel eluting with a mixture of 1% butanol–chloroform to yield the desired coupled products **28***a* and **28***b*. The less polar isomer, arbitrarily assigned structure **28***a* (1.78 g; 44% yield), was a glass, mp 104–106°C. The more polar isomer, arbitrarily assigned structure **28***b* (1.85 g, 45% yield), was a glass, mp 106–108°C.

**28***a*: ir (KBr) $\nu_{max}$: 3350 (NH amide), 1700, 1665 $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 1.40 (9H, s, —$C(CH_3)_3$), 2.10 (3H, s, $SCH_3$), 2.55 (4H, broad s, —$CH_2CH_2$—S—), 3.73 (3H, s, $OCH_3$), 4.13 (1H, m, tyrosyl methyne), 5.33 (b d, exchanged by $D_2O$, $J$ = 8 Hz, tyrosyl NH—BOC), 5.53 (1H, broad, NH amide, exchanged by $D_2O$), 6.80 (4H, $A_2B_2$ quartet, tyrosyl aromatics), 7.10 (5H, s, aromatics), 7.85 (s, 1H, OH, exchanged by $D_2O$).

**28***b*: ir (KBr) $\nu_{max}$: 3340, 1700, 1660 $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 1.37 (9H, s, —$C(CH_3)_3$), 2.07 (3H, s, $SCH_3$), 2.53 (4H, b, $CH_2CH_2S$), 3.68 (3H, s, $OCH_3$), 4.18 (1H, m, tyrosyl methyne), 5.20 (1H, d, $J$ = 8 Hz, tyrosyl—NH—BOC, exchanged by $D_2O$), 5.97 (1H, broad, NH amide, exchanged by $D_2O$), 6.77 (4H, $A_2B_2$ quartet, tyrosyl aromatics), 7.07 (5H, s, aromatics), 7.97 (s, 1H, OH, exchanged by $D_2O$).

*The coupling of **27**b with* N-t-*BOC tyrosine*

Similarly, reacting the *Z* isomer **27***b* (2.5 g) with *t*-BOC tyrosine (3.46 g), dicyclohexylcarbodiimide (2.53 g), and 1-hydroxybenzotriazole (1.9 g) in methylene chloride (125 mL) afforded after extraction with ether 5.7 g of a crude mixture of diastereoisomers that was separated by chromatography on silica gel.

**28***c*: (less polar diastereoisomer), 1.5 g (39%) as a glass, mp 100–104°C; ir (KBr) $\nu_{max}$: 3350, 1700, 1660 $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 1.40 (9H, s, *t*-Bu), 2.08 (3H, s, $SCH_3$), 2.57 (4H, broad s, $CH_2CH_2S$), 3.67 (3H, s, $OCH_3$), 4.17 (1H, m, tyrosyl methyne), 5.23 (1H, $J$ = 8 Hz, d, NH—BOC, exchanged by $D_2O$), 6.17 (1H, b, amide NH, exchanged by $D_2O$), 6.80 (4H, $A_2B_2$ quartet, $J_{AB}$ = 8 Hz, tyrosyl aromatic), 7.05 (5H, s, aromatic), 7.85 (1H, b s, OH, exchanged by $D_2O$).

**28***d*: (more polar diastereoisomer), 1.22 g (31%) as a glass, mp 108–111°C; ir (KBr) $\nu_{max}$: 3350, 1700, 1660 $cm^{-1}$; $^1$Hmr ($CDCl_3$) δ: 1.40 (9H, s, *t*-Bu), 2.07 (3H, s, $SCH_3$), 2.53 (4H, b s, $CH_2CH_2S$), 3.67 (3H, s, $OCH_3$), 4.2 (1H, m, tyrosyl methyne), 5.13 (1H, d, $J$ = 8 Hz, NH—BOC exchanged by $D_2O$), 5.90 (1H, b s, NH amide, exchanged by $D_2O$), 6.80 (4H, $A_2B_2$ quartet, $J_{AB}$ = 8 Hz, tyrosyl aromatic), 7.07 (5H, s, aromatic), 7.40 (1H, b s, OH, exchanged by $D_2O$).

[1]Tables 1, 2, and 3 are available, at a nominal charge, from the Depository of Unpublished Data, CISTI, National Research Council of Canada, Ottawa, Ont., Canada K1A 0S2.

*The four isomers of* trans-*methyl-2-(decahydro-4β-(phenylmethyl)-8β-(L-tyrosylaminomethyl)-2-naphthalenylidene)-4-(methylthio)butanoate HCl monohydrate* **1**a–d

The blocked derivatives **28***a–d* dissolved in chloroform (25 mL) were saturated with anhydrous hydrogen chloride and the resulting mixtures were stirred at room temperature for one hour. In each case the excess hydrogen chloride was blown off with a stream of nitrogen and the chloroform solution was washed with sodium bicarbonate and with water. The organic phase was dried over sodium sulfate and evaporated to dryness, leaving a residue which was purified by preparative hplc, eluting with 3% methanol–chloroform. The resulting derivative was taken up in chloroform, treated with hydrogen chloride, and evaporated to dryness. The residue was triturated in ether and filtered. Thus **28***a* (1.68 g) gave **1***a* (1.37 g; 89%), mp 154–156°C, $[\alpha]_D^{22}$ 0 (*c* 1.0, MeOH); ir (KBr) $\nu_{max}$: 3500–2600 ($NH_3^+$), 1700, 1670 $cm^{-1}$; $^1$Hmr ($CDCl_3$) (on free base) δ: 2.10 (3H, s, $SCH_3$), 2.57 (4H, s, $CH_2CH_2S$), 3.73 (3H, s, $OCH_3$), 3.80 (3H, $NH_2$ and OH, exchanged by $D_2O$), 6.90 (4H, $A_2B_2$ quartet, $J = 8$ Hz, tyrosyl aromatics), 7.13 (5H, s, aromatic), 7.45 (1H, b, amide NH, exchanged by $D_2O$); *m/e*: 564 ($M^+$), 503 ($M^+ - CH_2SCH_3^+$). *Anal.* calcd. for $C_{33}H_{44}N_2O_4S.HCl.\frac{1}{2}H_2O$: C 64.83, H 7.71, N 4.65; found: C 64.95, H 7.59, N 4.59.

Similarly **28***b* (1.77 g) gave **1***b* (1.30 g; 80%), mp 162–164°C, $[\alpha]_D^{22}$ +67.7° (*c* 1.0, MeOH); ir (KBr) $\nu_{max}$: 3500–2600 ($NH_3^+$), 1700, 1670 $cm^{-1}$; $^1$Hmr ($CDCl_3$) (on free base) δ: 2.10 (3H, s, $SCH_3$), 2.57 (4H, s, $CH_2CH_2S$), 3.73 (3H, s, $OCH_3$), 3.70 (3H, $NH_2$ and OH, exchanged by $D_2O$), 6.87 (4H, $A_2B_2$ quartet, $J = 8$ Hz, tyrosyl aromatic), 7.10 (5H, s, aromatic), 7.40 (1H, b s, NH amide, exchanged by $D_2O$); *m/e*: 546 ($M^+$), 503 ($M^+ - CH_2SCH_3$). *Anal.* calcd. for $C_{33}H_{44}N_2O_4S.HCl.\frac{1}{2}H_2O$: C 64.83, H 7.71, N 4.65; found: C 64.53, H 7.58, N 4.54.

Similarly, **28***c* (1.5 g) gave **1***c* (0.75 g; 54%), mp 149–151°C, $[\alpha]_D^{22}$ −17.1° (*c* 1.0, MeOH); ir (KBr) $\nu_{max}$: 3500–2600 ($NH_3^+$), 1700, 1670 $cm^{-1}$; $^1$Hmr ($CDCl_3$) (free base) δ: 2.10 (3H, s, $SCH_3$), 2.57 (4H, s, $CH_2CH_2S$), 3.73 (3H, s, $OCH_3$), 3.70 (3H, $NH_2$ and OH, exchanged by $D_2O$), 6.87 (4H, $A_2B_2$ quartet, $J = 8$ Hz, tyrosyl aromatic), 7.10 (5H, s, aromatic), 7.40 (1H, b s, NH amide, exchanged by $D_2O$), 7.47 (1H, b s, NH amide, exchanged by $D_2O$); *m/e*: 564 ($M^+$), 503 ($M - CH_2SCH_3$). *Anal.* calcd. for $C_{33}H_{44}N_2O_4S.HCl$: C 65.92, H 7.54, N 4.66; found: C 65.78, H 7.62, N 4.50.

Similarly, **28***d* (1.15 g) gave **1***d* (0.750 g; 54%), mp 157–160°C, $[\alpha]_D^{22}$ +79.1° (*c* 1.0, MeOH); ir (KBr) $\nu_{max}$: 3500–2600 ($NH_3^+$), 1700, 1670 $cm^{-1}$; $^1$Hmr ($CDCl_3$) (free base) δ: 2.13 (3H, s, $SCH_3$), 2.57 (4H, s, $CH_2CH_2S$), 3.60 (3H, $NH_2$ and OH, exchanged by $D_2O$), 3.70 (3H, s, $OCH_3$), 6.87 (4H, $A_2B_2$ quartet, $J = 8$ Hz, tyrosyl aromatic), 7.13 (5H, s, aromatic), 7.57 (1H, b s, NH amide, exchanged by $D_2O$); *m/e*: 546 ($M^+$), 503 ($M - CH_2SCH_3$). *Anal.* calcd. for $C_{33}H_{44}N_2O_4S.HCl.\frac{1}{2}H_2O$: C 64.83, H 7.71, N 4.65; found: C 65.33, H 7.86, N 4.48.

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