the unusual TMSI and Lewis acid catalyzed rearrangements and applications of this technology to natural product synthesis form the focus of our current endeavors and will be reported in due course.

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Supplementary Material Available: Experimental Section with ^1H and ^{13}C NMR spectra (including 2D NMR for **9a**, **9b**, **12a**, and **25**) and the details of preparation of compounds **5**, **6a,b**, **8**, **9a,b**, **11**, **12a,b**, **14**, **15a,b**, **17**, **18**, **20**, **21**, **25** (41 pages). Ordering information is given on any current masthead page.

A Four-Step Synthesis of TIBO R82150

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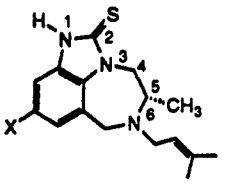
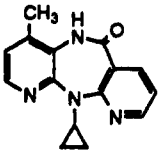
Summary: An efficient, four-step synthesis of the novel HIV-1 reverse transcriptase inhibitor TIBO R82150 is described.

The recently reported TIBO compounds, for example R82150 (**1a**) and R82913 (**1b**), are remarkably specific inhibitors of HIV-1 virion replication in T-cell cultures. Unlike AZT and the related nucleoside antiviral agents DDC and DDI, which are effective against both HIV-1 and HIV-2, the TIBO compounds do not inhibit replication of HIV-2, other RNA viruses, or DNA viruses. Several members of the TIBO series are active at nanomolar concentrations and TIBO **1b** has an inhibitory concentration equal to that of AZT. In preliminary tests in humans, TIBO **1a**, which has the best selectivity index (50% cytotoxic dose/50% inhibitory concentration) of the TIBO's reported, appears to be well tolerated.[1]



1a X=H, TIBO R82150
1b X=Cl, TIBO R82913

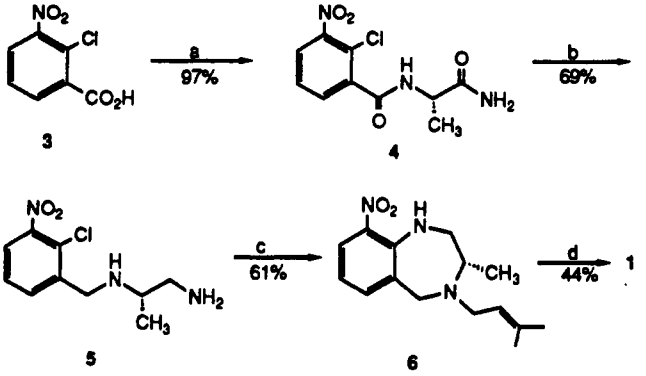


2, BI-RG-587

Since the discovery of the TIBO's, a second class of HIV-1 specific inhibitors, the dipyridodiazepinones (e.g. BI-RG-587, **2**) has been described.[2] The TIBO's and the dipyridodiazepinones inhibit HIV-1 reverse transcriptase; they do so by binding to a common site which is not a substrate binding site.[3] A third class of HIV-1-selective inhibitors appears to act by a different mechanism.[4]

The preparation of TIBO R82150 was originally reported to be an 11-step procedure with an overall yield of 4%.[1,5]

Scheme I. Synthesis of TIBO 1[a]



[a] (a) $(ClCO)_2$, PhMe, 50 °C; then L-alaninamide hydrochloride, K_2CO_3, PhMe/H_2O, 0 °C, 2 h; (b) 10 equiv of BH_3SMe_2, THF, reflux, 12 h; (c) DMF, K_2CO_3, 120 °C, 3-methyl-2-butenyl bromide; (d) H_2, 5% Pd(C), EtOH, 2 h, filter; then CS_2, 37 °C, 3 h.

Clearly, a shorter and more efficient synthesis of the TIBO structure was desirable for the preparation of analogues and essential for the anticipated manufacture of a drug in this series.

We are now pleased to report an efficient synthesis of TIBO R82150 in which the four structural components are incorporated into the desired TIBO product in only *four steps*. The synthesis uses only standard reagents, none of which is difficult to handle.

Straightforward retrosynthetic analysis of TIBO **1** strongly suggests precursors to three of its four structural components. Thus, the imidazothione ring would be elaborated by "capping" an aminodiazepine with a thiocarbonyl reagent; the C-4 to N-6 chain, containing the chiral center, would be derived from an L-alanine derivative; and the prenyl side chain would be introduced by alkylation of the benzylic nitrogen (N-6).

Recognition that commercially available 2-chloro-3-nitrobenzoic acid (**3**) might be a suitable precursor to the 1,2,3-trisubstituted benzene moiety led us to pursue a strategy in which the chloro substituent is displaced in an intramolecular nucleophilic aromatic substitution. Prep-

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(5) A shorter, recently-reported approach to the 2-oxo-TIBO compounds requires eight steps from commercially available material. See: Kukla, M. J.; Breslin, H. J.; Pauwels, R.; Fedde, C. L.; Miranda, M.; Scott, M. K.; Sherrill, R. G.; Raeymaekers, A.; Van Gelder, J.; Andries, K.; Janssen, M. A. C.; De Clercq, E.; Janssen, P. A. J. *J. Med. Chem.* **1991**, *34*, 746.

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aration of the substrate for this cyclization required two steps.

Treatment of benzoic acid 3 with oxaloyl chloride and addition of the reaction mixture to L-alaninamide gave crystalline diamide 4 (Scheme I). Selective reduction of the two amide groups in the presence of the nitro and chloro substituents was easily accomplished with $BH_3 \cdot SMe_2$ in refluxing THF.[6]

Cyclization to an intermediate tetrahydrobenzodiazepine was effected by heating crude diamine 5 in DMF containing solid K_2CO_3; regiospecific alkylation of the more nucleophilic amino group was accomplished by adding 3-methyl-2-butenyl bromide to the reaction mixture. This one-pot procedure afforded the penultimate product 6.

The nitro group of tetrahydrobenzodiazepine 6 was selectively hydrogenated in the presence of the side-chain olefin; after removal of the palladium catalyst by filtration, carbon disulfide was added and the resulting reaction mixture was heated. In the one-step procedure,[7] the nitro group was reduced and the resulting ortho diamine was capped with the thiocarbonyl group.

This four-step route, based on intramolecular nucleophilic aromatic substitution, provided the title compound 1a[8,9] in *18% overall yield* from commercially available 3. We anticipate that this efficient sequence will provide rapid access to a large number of novel TIBO analogues.

Acknowledgment. This research was supported by a grant from the National Institutes of Health (AI-29900), by a University Biomedical Research Support Grant (BRSG), and by Brown University.

Supplementary Material Available: Experimental procedures for the preparation of compounds 1, 4, 5, and 6 as well as spectra (^1H NMR, ^{13}C NMR and IR) for 1, 4, and 6 (13 pages). Ordering information is given on any current masthead page.

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(9) The activity of TIBO R82150 in T4 lymphocytes (CEM cell line) was confirmed in the NIH screen. We are grateful to Drs. Robert Schultz and Mohamed Nasr for expediting in vitro testing of our compounds.

Radical Mediated Intramolecular [3-Atom + 2-Atom] Addition and the Synthesis of (±)-Rocaglamide: Model Studies

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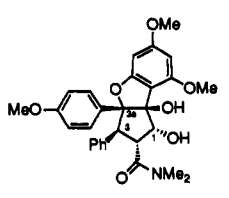
Summary: The cyclopenta[*b*]benzofuran ring system of the antileukemic natural product rocaglamide can be efficiently prepared by intramolecular [3 + 2] radical mediated addition. The stereochemical relationship that emerges between C(2) and C(3a) upon cyclization is identical with that seen in the natural product.

Rocaglamide (1) is the agent responsible for the antileukemic activity of extracts from the roots and stems of *Aglaia elliptifolia*.[1] Its structure, determined by single-crystal X-ray analysis, was reported in 1982,[1] and very recently its absolute stereochemistry was found to be as shown by total synthesis of the naturally occurring antipode.[2] The structural complexity of rocaglamide, coupled with its powerful biological activity,[1,3] combine to make it an attractive target for total synthesis.[4] Herein we report an efficient synthesis of the tricyclic cyclopenta[*b*]benzofuran framework of rocaglamide, as part of a study directed toward the total synthesis of this unique natural product.



1

Recently we have disclosed a radical mediated [3 + 2] addition methodology for the synthesis of substituted cyclopentanes utilizing functionalized vinylcyclopropanes and alkenes as reaction partners.[5] Substitution of an alkyne for the alkene allows for the efficient construction of cyclopentenes,[6] and we felt that an intramolecular variant of this latter reaction would be ideally suited for the construction of the rocaglamide skeleton.

To test such an hypothesis, we first synthesized the diastereomeric vinylcyclopropanes 6 in a straightforward six-step procedure (Scheme I).[7] Exposure of a benzene solution of diphenyl disulfide and either diastereomer of 6 (or a mixture of both diastereomers) to sunlamp irradiation affected smooth transformation to the cyclopenta[*b*]benzofuran system 7 in 94% yield. Notably, only

6 7

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