JOURNAL OF combinatorial CHEMISTRY

Report

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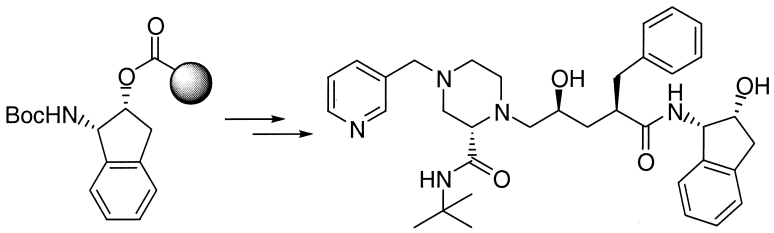
J. Comb. Chem., **2000**, 2 (5), 445-446• DOI: 10.1021/cc000029z • Publication Date (Web): 25 August 2000



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Solid Phase Synthesis of Indinavir and Its Analogues

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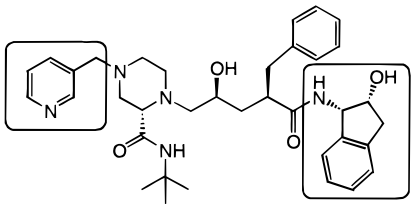
Received April 14, 2000

Indinavir is one of the five potent HIV protease inhibitors that have been approved by the U.S. Federal Drug Administration as key therapeutic agents for the treatment of HIV infection and AIDS.[1] Although these agents have been shown to be efficacious, they all suffer to some degree from short half-life and increasing viral resistance.[2] To improve potency and physical properties as well as the pharmacokinetic profile, we were interested in developing a facile synthesis to generate indinavir analogues rapidly. Herein we report the first solid phase synthesis of indinavir and its analogues, which paves the way for the generation of combinatorial libraries for biological screening and pharmacokinetic studies.[3]

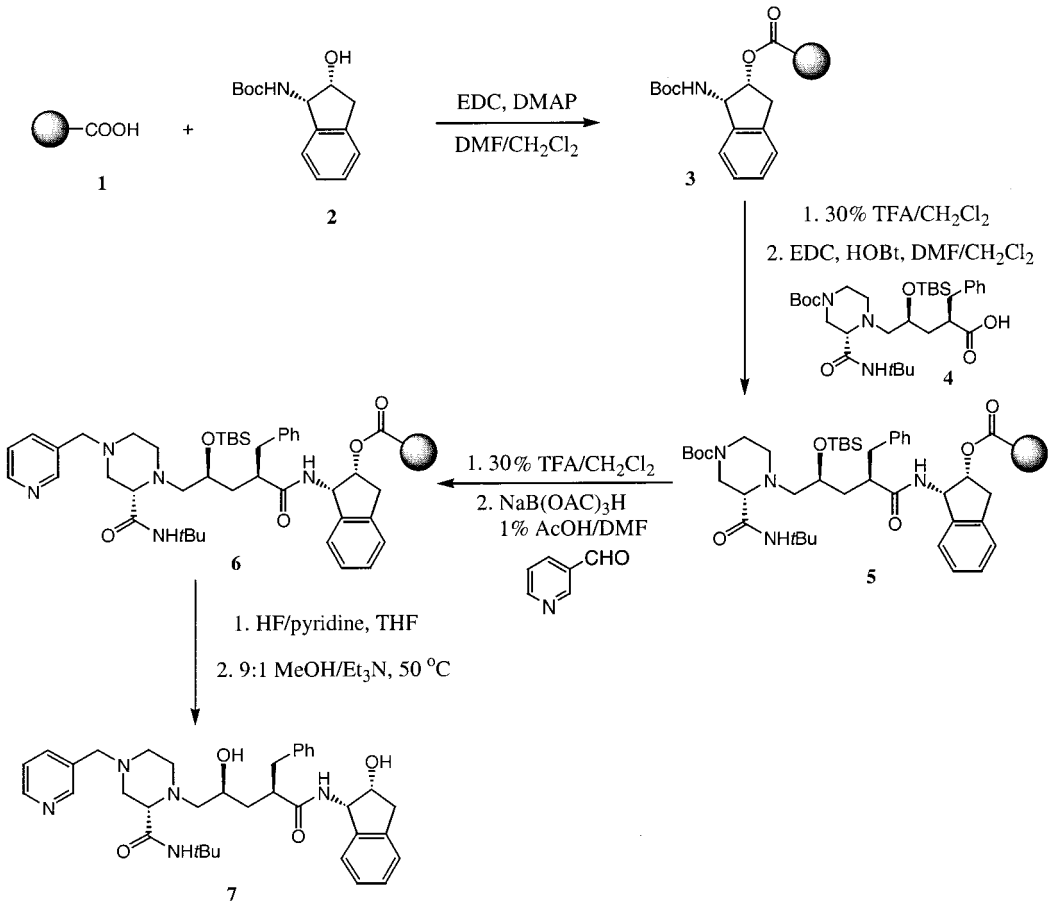
The total synthesis of indinavir in solution is a well-known challenge due to its structural complexity.[4] The solid phase synthesis of indinavir required us to develop a general synthetic strategy that would allow us to explore diversity at sites known to be metabolized, alter efficacy, and change physical properties.



We decided to divide the indinavir molecule into three fragments, the aminoindanol moiety, the hydroxyethylene unit, and the pyridylmethyl group. The hydroxyl group on aminoindanol was used as a resin tether which was attached to the Rapp TentaGel S COOH resin via an ester linkage. The hydroxyethylene and pyridylmethyl fragments could be coupled sequentially through amide formation and reductive amination. The final product could be cleaved from the resin by transesterification with mild base. This approach is straightforward for facile diversification of all three fragments.

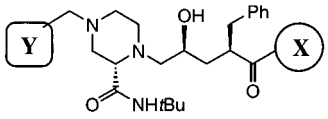
Our solid phase synthesis of indinavir is illustrated in Scheme 1. Boc protected aminoindanol **2** was coupled to the resin (0.25 mmol/g) with EDC and DMAP in DMF and

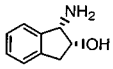
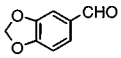
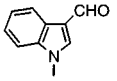
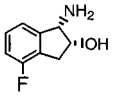
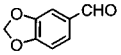
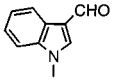
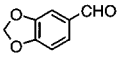
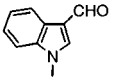
Scheme 1



10.1021/cc000029z CCC: $19.00
Published on Web 08/25/2000

Table 1. Solid Phase Synthesis of Indinavir Analogues



Entry	X	Y	Yield[a]	HPLC Purity
a			71%	>95%
b			80%	>95%
c			83%	91%
d			71%	92%
e			80%	>95%
f			83%	84%
g			84%	88%
h			87%	>95%
i			77%	70%
j			86%	81%
k			77%	84%
l			71%	86%

[a] Yields are calculated based on theoretical loading.

CH_2Cl_2 (1:4) to afford **3**. After removing the Boc protecting group with TFA/CH_2Cl_2, the resin was neutralized with 30% Et_3N/CH_2Cl_2 during the washing cycle. The TBS protected hydroxylethylene fragment **4**[5] was coupled to **3** by standard amide formation protocol. Then the Boc group was removed, the pyridylmethyl moiety was incorporated by reductive amination using $NaB(OAc)_3H$ in 1% AcOH/DMF to give **6** which was treated with HF/pyridine to remove the TBS group. The final product was cleaved from the resin with 10% Et_3N/MeOH at 50 °C overnight. Indinavir was obtained in good yield and excellent chemical purity as determined by HPLC,[6] ^1H NMR, and LC-MS analysis (Table 1, entry b).

Using this methodology, several indinavir analogues were prepared on solid support (Table 1). All the compounds are produced in purities of greater than 70%, which demonstrated the versatility and efficiency of the indinavir syntheses described herein.

In summary, a novel solid phase synthesis of indinavir and its derivatives has been developed. The method is versatile and ideally suitable for combinatorial library generation. Therefore, this approach offers the potential of providing diverse libraries of indinavir derivatives for biological assays.

Acknowledgment. We thank Nathan A. Yates and Amy M. Bernick for performing LC-MS analysis and the Department of Process Research for providing aminoindanol fragments.

Supporting Information Available. General experimental procedures and characterization data for indinavir analogues are available free of charge via the Internet at http://pubs.acs.org.

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(5) Methods used to prepare this intermediate are described in ref 4a.

(6) Analysis by HPLC using a 4.6 × 50 mm YMC Combiscreen C18 column (5 μm particle size) with a gradient of 10% acetonitrile/water containing 0.1% TFA to 100% acetonitrile over 2.25 min. Peak areas were integrated at 220 nm.

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