TABLE 4. Anti-HIV Activities of the Synthetic Compounds against HIV-1 Clinical Isolates

			IC_{50} (nM) (fold change)[a] MDR[b]		
run	compd	$HIV_{ERS104pre}$	HIV_{TM}	HIV_{MM}	HIV_{JSL}
1	**12d**	230 ± 30	>1000 (>4 x)	>1000 (>4 x)	NT
2	**13d**	24 ± 0.1	>1000 (>42 x)	>1000 (>42 x)	NT
3	**14d**	33 ± 5	>1000 (>32 x)	>1000 (>32 x)	NT
4	**12e**	24 ± 4	240 ± 190 (10 x)	100 ± 80 (5 x)	290 ± 70 (12 x)
5	**14e**	34 ± 13	260 ± 190 (8 x)	340 ± 20 (10 x)	410 ± 80 (11 x)
6	saquinavir	19 ± 4	230 ± 20 (12 x)	320 ± 2 (17 x)	550 ± 160 (29 x)
7	amprenavir	20 ± 3	480 ± 120 (24 x)	530 ± 80 (27 x)	800 ± 70 (40 x)

[a] IC_{50} values are based on inhibition of HIV p24 antigen expression in PBMC. All values represent the means from at least three independent experiments. Data without standard deviations are derived from the value for one experiment. [b] Amino acid substitutions in the protease-encoding region are shown in Supporting Information.

Among the compounds synthesized by using our method, **12d−14d** each have a decahydroisoquinoline unit, which is present in saquinavir[30,32] and nelfinavir,[33] at the P_1'−P_2' position (Scheme 6). Compounds **12e** and **14e** also each have a sulfonamide unit, which is present in amprenavir,[34] at the P_1'−P_2' position.

The anti-HIV activity of compounds **12d−14d**, **12e**, and **14e** was determined on the basis of inhibition of HIV-1-induced cytopathogenicity in MT-2 cells (described in Supporting Information).[35] Compounds **13d** and **14d** showed potent anti-HIV activity (Table 3, runs 2 and 3). They proved to be more potent than saquinavir (run 6) and amprenavir (run 7), which have currently been used clinically. It was noted that compounds **12d−14d**, **12e**, and **14e** (runs 1−5) exhibited greater selectivity indices (SIs) than saquinavir (run 6).

Next, we determined the anti-HIV activity of compounds **12d−14d**, **12e**, and **14e** against multidrug-resistant (MDR) strains as measured by the inhibition of HIV p24 antigen expression in peripheral blood mononuclear cells (PBMC) (described in Supporting Information).[35] The efficacy against $HIV_{ERS104pre}$ and three MDR strains of compounds **12e** and **14e** was similar to that of saquinavir and amprenavir (Table 4, runs 4−7).

Conclusion

In summary, we have found a novel indium-mediated atom-transfer radical cyclization reaction using a catalytic amount of In with I_2 and reductive radical cyclization reaction using an excess amount of In and I_2 without the use of a radical initiator such as AIBN or Et_3B/O_2. The protocol described above provides a new methodology for multibond formation and enables division of geometrical isomers. Novel HIV protease inhibitors, **12d−14d**, **12e**, and **14e**, were synthesized using the indium-mediated reductive radical cyclization method. They all inhibited HIV-induced cytopathogenicity in MT-2 cells and were all as effective as saquinavir and amprenavir against MDR strains. The present results will be useful for developing new attractive aspects of indium chemistry.

Experimental Section

General. Indium-Mediated Atom-Transfer Cyclization of Iodoalkyne (1) (condition A). The mixture of iodoalkyne **1** (2 mmol), In (2 mmol), and I_2 (1 mmol) in MeOH (4 mL) was stirred for 5 h at room temperature under nitrogen. MeOH was evaporated, and the residue was filtered with Celite using chloroform as an eluent. The filtrate was concentrated. The residue was purified by flash silica gel column chromatography to afford compound **1a** (404 mg, 76%), **1b** (21 mg, 4%), and **1c** (8 mg, 3%).

Indium-Mediated Reductive Radical Cyclization of Iodoalkyne (1) (condition B). The mixture of iodoalkyne **1** (2 mmol), In (4 mmol), and I_2 (2 mmol) in MeOH (4 mL) was stirred for 17 h at room temperature under nitrogen. MeOH was evaporated, and the residue was filtered with Celite using chloroform as an eluent. The filtrate was concentrated. The residue was purified by flash silica gel column chromatography to afford compound **1c** (238 mg, 85%) as an yellow oil.

Acknowledgment. This work was supported in part by The Japan Health Sciences Foundation, by a Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Science, Sports, and Culture, Japan, and by 21st Century COE Program "Knowledge Information Infrastructure for Genome Science".

Supporting Information Available: Experimental procedures and characterization data of synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035482M

(29) Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656−3664.

(30) Ghosh, A. K.; Kincaid, J. F.; Cho, W.; Walters, D. E.; Krishnan, K.; Hussain, K. A.; Koo, Y.; Cho, H.; Rudall, C.; Holland, L.; Buthod, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 687−690.

(31) Kaldor, S. W.; Kalish, V. J.; Davies, J. F., II; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979−3985.

(32) Ghosh, A. K.; Thompson, W. J.; McKee, S. P.; Duong, T. T.; Lyle, T. A.; Chen, J. C.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 292−294.

(33) Martin, J. A.; Redshaw, S. Eur. Pat. Appl. EP 432,695, June 19, 1991.

(34) Ghosh, A. K.; Thompson, W. J.; Holloway, M. K.; Mckee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 2300−2310.

(35) Koh, Y.; Nakata, H.; Maeda, K.; Ogata, H.; Bilcer, G.; Devasamudram, T.; Kincaid, J. F.; Boross, P.; Wang, Y. F.; Tie, Y.; Volarath, P.; Gaddis, L.; Harrison, R. W.; Weber, I. T.; Ghosh, A. K.; Mitsuya, H. *Antimicrob. Agents Chemother.* **2003**, *47*, 3123−3129.